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Cost-effectiveness of Guided Internet-Delivered Cognitive Behavioral Therapy in Comparison with Care-as-Usual for Patients with Insomnia in General Practice

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ABSTRACT

Study objectives: Clinical guidelines recommend cognitive-behavioral therapy for insomnia (CBT-I) as first-line treatment. However, provision of CBT-I is limited due to insufficient time and expertise. Internet-delivered CBT-I might bridge this gap. This study aimed to estimate the cost-effectiveness of guided, internet-delivered CBT-I (i-Sleep) compared to care-as-usual for insomnia patients in general practice over 26 weeks from a societal perspective.

Methods: Primary outcomes were the Insomnia Severity Index (ISI, continuous score and clinically relevant response), and Quality-Adjusted Life Years (QALYs). Societal costs were assessed at baseline, and at 8 and 26 weeks. Missing data were imputed using multiple imputation. Statistical uncertainty around cost and effect differences was estimated using bootstrapping, and presented in cost-effectiveness planes and acceptability curves.

Results: The difference in societal costs between i-Sleep and care-as-usual was not statistically significant (-€318; 95% CI −1282 to 645). Cost-effectiveness analyses revealed a 95% probability of i-Sleep being cost-effective compared to care-as-usual at ceiling ratios of €450/extra point of improvement in ISI score and €7,000/additional response to treatment, respectively. Cost-utility analysis showed a 67% probability of cost-effectiveness for i-Sleep compared to care-as-usual at a ceiling ratio of 20,000 €/QALY gained.

Conclusions: The internet-delivered intervention may be considered cost-effective for insomnia severity in comparison with care-as-usual from the societal perspective. However, the improvement in insomnia severity symptoms did not result in similar improvements in QALYs.

Introduction

Insomnia is an important public health problem. Approximately one-third of the general population has symptoms of insomnia, while about 10% of the population meets all diagnostic criteria for an Insomnia Disorder. This makes insomnia the second most-prevalent mental disorder in the general population next to depression (Wittchen et al., 2011). The economic burden of insomnia to society is substantial, because individuals with insomnia use more healthcare services and have more functional impairments. Previous research has shown that participants with insomnia cost approximately 10 times more than good sleepers due to increased healthcare utilization, higher rates of absenteeism

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from paid work and associated lost productivity costs (Daley et al., 2009a, 2009b). Participants suffering from insomnia are also at higher risk of developing comorbid mental health problems, such as depression and anxiety, and cardiovascular health issues which increase the risk of premature mortality (Li et al., 2018; Olfson et al., 2018; Sofi et al., 2014).

Previous research has shown that cognitive-behavioral treatment for insomnia (CBT-I) is effective in reducing insomnia severity, also in the primary care setting (Cheung et al., 2019; Van Straten et al., 2018). CBT-I is, therefore, recommended as the first-line treatment for insomnia (Nederlands Huisartsen Genootschap [NHG] Richtlijnen, 2014; Qaseem et al., 2016; Riemann et al., 2017; The National Institute for Health and Care Excellence [NICE], 2004). Despite the considerable evidence supporting the effectiveness of CBT-I, general practitioners (GPs) primarily tend to prescribe medication (Everitt et al., 2014). A possible explanation is that GPs themselves often do not have enough time or expertise (Edinger & Wohlgemuth, 1999; Everitt et al., 2014; Morin et al., 2006). Furthermore, there is a lack of qualified psychologists to refer insomnia patients to. Internet-delivered CBT-I presents a promising solution for this problem.

Existing clinical trials and meta-analyses have reported comparable effects between online CBT-I and face-to-face treatment (Andersson et al., 2014; Espie et al., 2019). However, results from direct comparisons between the two treatments are mixed, indicating no differences or superior effect sizes of face-to-face treatments over online CBT-I (Blom et al., 2015; Lancee et al., 2016). The effectiveness of internet-delivered treatments generally increases when delivered with some form of support (Lancee et al., 2013, 2012). Furthermore, two previous studies showed that there is a high probability of internet-based CBT-I being cost-effective compared to care-as-usual (De Bruin et al., 2016; Thiart et al., 2016).

It has been observed that adherence to internet-delivered CBT for insomnia and depression is related to some administrative or therapist guidance (Espie et al., 2019; Horsch et al., 2015; Van Ballegooijen et al., 2014). In the Netherlands, 90% of general practices employ mental health nurse practitioners (MHNPs), usually psychiatric nurses, or young psychologists whose task is to support patients with mild mental health symptoms in face-to-face consultations. Those MHNPs are optimal candidates to provide this support for online treatment of insomnia in the general practice. The online support usually takes about 1.5 hour per patient. Therefore, the costs of delivering online CBT-I are generally expected to be lower than face-to-face CBT-I (usually four to six sessions). Thus, provision of guided internet-delivered CBT-I within their own practice will allow GPs to provide patients with guideline-concordant care while efficiently using limited resources.

The aim of this study was to evaluate the cost-effectiveness (outcome measures expressed in improvement in severity symptoms) and cost-utility (outcome measures expressed in Quality Adjusted Life Years; QALYs) of an internet-delivered CBT-I compared to care-as-usual for participants with insomnia treated in general practice from a societal perspective. Van der Zweerde et al. recently showed that this guided, internet-delivered CBT-I resulted in greater improvements in insomnia severity compared to care-as-usual both at post treatment and at 26 weeks follow-up (Van Der Zweerde et al., 2020). We expected that the internet-delivered intervention would not only reduce insomnia severity, but also societal costs, while improving quality of life as compared to care-as-usual.

Methods

Study design

This economic evaluation was conducted alongside a pragmatic randomized controlled trial comparing internet-delivered cognitive-behavioral therapy (i-Sleep) with care-as-usual in general practice participants with insomnia. The time horizon was set at 26 weeks and the analysis was conducted from a societal perspective. Costs and effects were collected at baseline, and at 8 and 26 weeks of follow-up. This trial was approved by the Medical Ethics Review Committee of the VU Medical Center

Amsterdam and is registered in the Dutch Trial Register (http://www.trialregister.nl/trialreg/index.asp, identifier: NTR5202). The study design has been presented in detail in the study protocol and will be briefly described here (Van der Zweerde et al., 2016).

Population

Between October 2015 and April 2018, insomnia patients were recruited through general practices. Half of the participating practices were recruited through the Amsterdam General Practitioner Network (N = 8). During the trial, an additional convenience sample was pursued due to low inclusion rates (N = 7). The 15 practices occupied a total of 50 GPs and 20 MHNPs over the 2.5 year inclusion period of the trial. Although GPs were predominately responsible for recruitment, MHNPs also participated in the process by referring patients they were already working with to the trial website or the GP.

Recruitment leaflets directing potential participants to the trial website were distributed in print in the waiting rooms of general practices, and in GPs' and MHNPs' consulting rooms. Study information was also displayed on television screens in the general practices that had such screens. GPs and MHNPs in participating practices were also asked to notify their (suspected) insomnia patients for the trial. Additionally, GPs approached patients who received consultation for insomnia within the past year by sending them the leaflet via e-mail. Individuals interested in participating were screened using an online questionnaire.

Eligible participants were 1) 18 years or older; 2) had access to the Internet; 3) had adequate proficiency in Dutch; and 4) met the DSM-5 criteria for insomnia disorder (American Psychiatric Association, 2013). Potential participants were requested to complete an online questionnaire in which the following DSM-5 criteria were assessed: a) difficulty initiating or maintaining sleep for ≥ 30 minutes per night for ≥ 3 nights per week, and for at least 3 months; and b) causing clinically significant distress and/or impairment in daily functioning. The DSM-5 diagnosis of insomnia was not validated by a clinician during an interview. Distress was measured using items of the Daytime Consequences questionnaire developed by Espie and colleagues (Espie et al., 2012). The questionnaire consists of six items which measure the effect of insomnia on energy, relationships, mood, concentration, productivity, and sleepiness. Items were rated on a 5-point scale ranging from 0 (not affected at all) to 4 (very much affected). In order to be included in the trial, a score of at least 3 on at least one domain of the questionnaire was required.

Exclusion criteria were 1) pregnancy or breast feeding during participation; 2) working in night shifts; 3) other current psychological treatment; 4) being suicidal (assessed using 5 items from the MINI diagnostic interview (Sheehan et al., 1998), and 5) schizophrenia or psychotic disorder ("Have you been diagnosed with schizophrenia or psychosis", answered with "Yes" or "No"). Other comorbid psychological and somatic disorders were not used as an exclusion criterion and neither was the use of sleep medication. Eligible participants received a study brochure along with a sleep diary, informed consent form and stamped return envelope.

Randomization and sample size

Participants that returned completed sleep diaries and informed consent were randomized on a 1:1 ratio into either the i-Sleep or the care-as-usual group. Two independent researchers conducted the randomization, using a random allocation sequence, and allocated the included patients to one of the two groups. Randomization was stratified by medication use in the past month and MHNP practice in random blocks of two, four, and six. Due to the nature of the interventions, blinding participants or MHNPs to the treatment allocation was not possible. GPs were informed when participants were randomized to ensure they would receive care-as-usual. Assuming an effect size of Cohen's d = 0.50 on the Insomnia Severity Index (ISI) and a dropout risk of 20%, a sample size of 160 participants was needed to ensure sufficient statistical power (80%) (Cohen, 1988; Horsch et al., 2015). The inclusion phase of this trial has prematurely ended at 134 out of 160 participants due to other research on

insomnia planned in the participating GP practices. Based on the within-between group analysis and the sample size of n = 134 a power of 0.8 (alpha = .05) was obtained to detect an effect size of d = .24.

Internet-based intervention

The internet-delivered guided intervention, i-Sleep, is based on face-to-face cognitive-behavioral therapy for insomnia and includes the elements usually incorporated in this treatment (Edinger & Means, 2005; Edinger & Wohlgemuth, 1999; Espie, 2006; Morin & Espie, 2003; Verbeek & Klip, 2005). The i-Sleep intervention consists of five lessons with different topics: 1) psycho-education and (un)healthy sleep hygiene, 2) shortening time spent in bed and leaving the bed when awake (sleep restriction treatment and stimulus control), 3) relaxation exercises and rumination, 4) handling dysfunctional cognitive beliefs (about sleep and other) and 5) summary and relapse prevention. Participants had to fill out a sleep diary at every lesson and write down their plan for the coming period. Participants were advised to do one lesson a week and could only continue to a next lesson after finishing the previous one. The MHNP provided online written feedback every week on the homework and sleep diary. The aim of their feedback was to clarify information and motivate the participants to carry out the course and the requested behavioral changes. The structure of the intervention and content of the modules is described in more detail elsewhere (Van der Zweerde et al., 2016, 2020). Prior to the trial, MHNPs received training in using the i-Sleep program (1.5 hours) and in offering online guidance during the i-Sleep program. Further supervision from a specialized psychologist (TvdZ) was provided on an as needed basis. The time spent on giving online feedback was estimated at around 15–20 minutes per session. Participants in the i-Sleep group were also allowed to receive care-as-usual from their GP or MHNP.

Care-as-usual

The participants allocated to the control group received care-as-usual. GPs participating in the trial received a printed copy of the most recent Dutch GP insomnia guidelines which recommend cognitive-behavioral therapy for insomnia as the first line of treatment (Nederlands Huisartsen Genootschap [NHG] Richtlijnen, 2014). This ensured alignment of knowledge on the current sleeping treatments among the GPs. GPs were informed about participants who were randomized in the care-as-usual group, who were then invited to receive i-Sleep six months upon randomization. Care-as-usual provided by GPs was not restricted in any way throughout the trial; therefore, the content of the consultations in the care-as-usual group is unclear.

Clinical outcomes

Primary outcomes in this economic evaluation were the Insomnia Severity Index (ISI) (Bastien et al., 2001; Morin et al., 2011) and Quality-Adjusted Life-Years (QALYs). The continuous ISI score was assessed at baseline, post-treatment (8 weeks), and at follow-up (26 weeks). The ISI comprises seven items assessing the perceived sleep quality, insomnia nature and severity as well as its impact on physical and social functioning. Items are scored on a Likert scale from 0 (not at all) to 4 (extremely). Summed scores can range from 0 to 28, with higher scores indicating higher severity of insomnia (Bastien et al., 2001). Prior research has shown that ISI is a reliable tool with adequate internal consistency to measure perceived insomnia severity (Morin et al., 2011). It has also been validated for online use (Thorndike et al., 2011). The ISI was also used to calculate the percentage of participants with clinically relevant response to treatment. A clinically relevant response was defined as a change of ≥ 8 points in ISI score from baseline to follow-up (26 weeks) (Morin et al., 2011). The effectiveness outcomes for both i-Sleep and care-as-usual are extensively described in the clinical trial paper by van der Zweerde et al (Van Der Zweerde et al., 2020).

QALYs were calculated based on health-related quality-of-life measurements at baseline, and at 4, 8 and 26 weeks after baseline using the five-level version of the EuroQol (EQ-5D-5 L) (Herdman et al., 2011). The EQ-5D-5 L contains five dimensions (mobility, self-care, activities of daily living, pain/discomfort and depression/anxiety) with 5 answer levels (no problems to severe problems). The EQ-5D-5 L health states were converted to utility scores using the Dutch tariff, where 0 refers to death and 1 to full health (range −0.446 to 1, where negative utilities indicate that a health state is valued as worse than death) (Versteegh et al., 2016). The negative values of the tariff stem from the methods used to valuate health states; that is, in some cases, the respondents consider the health states they are presented with as "worse than death". Using the area under the curve method, QALYs were calculated by multiplying the amount of time a patient spent in a specific health state with the utility score associated with that health state. Transitions between health states were linearly interpolated.

Costs

Costs and healthcare utilization were assessed from a societal perspective using an adapted version of the Trimbos and i-MTA Questionnaire on Costs Associated with Psychiatric Illness (Tic–P) (Hakkaart-van Roijen et al., 2002). The Tic-P is a comprehensive, self-report questionnaire that focuses on estimating direct healthcare costs and productivity costs related to mental disorders. Existing evidence suggests that Tic-P is a feasible, well-understood tool that shows satisfactory reliability and construct validity in measuring visits to specialists and productivity losses (Bouwmans et al., 2013). The Tic-P questionnaire was administered at baseline, and at 8 and 26 weeks after baseline. The recall periods participants were asked to consider when reporting medication use, number of healthcare visits, and productivity losses were 1 month at baseline, 2 months at 8 weeks, and 4 months at 26 weeks after baseline.

Healthcare costs included all types of visits to primary care (e.g., general practitioner, physiotherapist) and secondary care (e.g., medical specialist, psychologist or psychiatrist, hospital admission), and medication costs. Costs of informal care consisted of patient and family costs. Informal care is defined as unpaid care provided by family members or volunteers to support patients with daily activities (e.g., eating, bathing, etc). These costs were calculated by multiplying the units of resource use by their unit price using standard costs from the Dutch costing guidelines (Hakkaart-van Roijen et al., 2015). Medication use was valued using prices from the Dutch Healthcare Institute on www.medicijnkosten.nl. Since no specific market price is available for the cost of informal care, a shadow price (i.e. proxy value) equal to the tariff of cleaning work was assumed (Hakkaart-van Roijen et al., 2015).

Lost productivity costs consisted of costs of absenteeism from paid and unpaid work, and presenteeism (i.e. an employee being present at work but not fully productive due to ongoing physical or mental conditions). Costs of absenteeism from paid work and presenteeism were valued using gender-specific incomes of the Dutch population and calculated according to the friction cost approach. This method assumes that within a specific time-span (i.e. friction period of 12 weeks), the sick employee is replaced and there are no more productivity losses thereafter (Hakkaart-van Roijen et al., 2015; Van den Hout, 2010). Absenteeism from unpaid work was calculated using the same shadow price as for informal care.

The costs of the i-Sleep intervention were calculated using a bottom-up approach. Costs that were included were 1) costs associated with using the online platform and 2) costs related to the time invested by the MHNPs in providing feedback, which depended on the number of completed lessons. Subscription costs to the online platform were assumed to be equal to €39, which is equal to the subscription costs per patient charged by a large organization hosting internet-delivered mental health interventions (Minddistrict). Costs of guidance by the MHNP were calculated using the standard reference price per consult by a MHNP (Hakkaart-van Roijen et al., 2015). All costs were in Euros and adjusted to the year 2018 using consumer price indices

if necessary (Statline Netherlands, 2020). Discounting was not necessary, since the follow-up period was 26 weeks. The cost categories and prices used in this economic evaluation are presented in more detail in the Supplementary Material of this paper.

Statistical analysis

All analyses were conducted according to the intention-to-treat principle. Missing cost and effect data were imputed using the Multiple Imputation with Chained Equations (MICE) algorithm with predictive mean matching (Van Buuren & Groothuis-Oudshoorn, 2011). Besides variables included in the analysis models, the imputation model included variables that 1) differed at baseline between treatment groups; 2) were related to the missingness of data; or 3) were associated with any of the outcomes. Predictor variables that were related to missingness included age, living situation, and quality of life as measured at baseline. Therefore, it was assumed that cost and effect data were missing at random (Faria et al., 2014). By multiple imputation (MI), 10 imputed datasets were created resulting in a loss of efficiency lower than 5% (White et al., 2011). Each imputed dataset was analyzed separately and results from the 10 datasets were pooled using Rubin's rules (Rubin, 1987).

Bivariate regression was performed to estimate cost and effect differences between the treatment groups, while accounting for potential correlation between the cost and effect outcomes (Willan et al., 2004). Incremental Cost-Effectiveness Ratios (ICERs) were calculated by dividing the difference in costs by the difference in effects between the groups. Bias-corrected and accelerated bootstrapping with 5000 replications was used to estimate 95% confidence intervals around the cost and effect differences (Efron, 1994). Statistical uncertainty surrounding the ICERs was graphically presented by plotting the bootstrapped incremental cost-effect pairs on a cost-effectiveness (CE) plane (Black, 1990).

Cost-effectiveness acceptability curves (CEACs) were also estimated, showing the probability that the i-Sleep intervention is cost-effective compared to care-as-usual for a range of different ceiling ratios (Fenwick et al., 2004). Analyses were performed using IBM SPSS Statistics 24® (IBM Corp., Armonk, NY, US) and StataSE 14® (StataCorp LP, CollegeStation, TX, US).

Sensitivity analysis

To check the robustness of the results, three sensitivity analyses were performed. The first sensitivity analysis was conducted from the healthcare (government) perspective, which is used for decision-making in other countries, such as the United Kingdom. The second sensitivity analysis concerned a per protocol analysis comprising only participants who completed all five sessions of the i-Sleep intervention and all patients randomized to the care-as-usual group. In the final sensitivity analysis, lost productivity costs due to absenteeism were calculated using the human capital instead of the friction cost approach which is more common in other countries. The friction cost method assumes that lost productivity costs are confined to the period needed to replace a sick worker, whereas the human capital method estimates lost productivity costs over the whole period of absence.

Results

Population

In total, 134 individuals who were willing to participate met the inclusion criteria and were randomized to the i-Sleep intervention group (n = 69) or care-as-usual (n = 65). In the i-Sleep group, 47 (68%) participants completed all five sessions of the i-Sleep intervention, 14 (20%) did not complete the treatment, and 8 (12%) never started the lessons. At 8 weeks, 56 (81%) and 55 (85%) participants

Table 1. Baseline characteristics.

Patient characteristics	i-Sleep (n = 69)	Care-as-usual (n = 65)
Age [(mean, (SD)]	51.74 (15.77)	49.40 (16.01)
Female (n, %)	43 (62)	44 (68)
Higher education (%)	76.8	60
Born in the Netherlands (n, %)	60 (87)	56 (86.2)
Living situation (n, %)		
Shared	45 (65.2)	31 (47.7)
Living with children (n, %)		
Yes	22 (31.9)	15 (23.1)
Working (n, %)		
Yes	35 (50.7)	39 (60)
Previous psychological treatment (n, %)	13 (18.8)	16 (24.6)
Prescribed sleep medication use (n, %)	23 (33)	25 (39)
Prescribed antidepressant use (n, %)	7 (10.1)	6 (9.2)
Total consequences [(mean, (SD)]	18.7 (3.5)	20 (3.2)
Baseline HADS score [mean, (SD)]		
Anxiety	8.2 (3.0)	8.4 (2.7)
Depression	6.0 (3.8)	6.6 (4.1)
Baseline ISI score [mean, (SD)]	19.0 (4.0)	19.4 (3.7)
Baseline EQ-5D-5 L utility score [mean, (SD)]	0.78 (0.15)	0.77 (0.20)

HADS: Hospital Anxiety and Depression Scale.

responded to the questionnaires in the i–Sleep and care-as-usual group, respectively. At the 26 weeks follow-up, the response was 53 (77%) and 54 (83%) respondents in the i-Sleep and care-as-usual groups, respectively. Baseline characteristics are presented in Table 1. Mean scores for daytime consequences were slightly higher for participants in the care-as-usual group. The flow of participants through the trial is shown in Figure 1.

Clinical outcomes

The multiply imputed clinical outcomes at 26 weeks follow-up are presented in Table 2. The mean pooled continuous ISI score in the i-Sleep group was statistically significantly lower than in the care-as -usual group (mean difference 3.9 points; 95%CI 1.6 to 6.3). The percentage of participants experiencing a clinically relevant response according to ISI at 26 weeks as compared to baseline in the i-Sleep group was statistically significantly higher than in the care-as-usual group (mean difference 28%; 95% CI 0.13 to 0.44). The mean pooled difference in QALYs over 26 weeks between the groups was 0.01, which was not statistically significant (95%CI −0.001 to 0.02).

Costs

Table 2 summarizes the pooled mean costs and the adjusted differences in costs between the two groups. Mean intervention costs were on average €99 per patient in the i-Sleep group, including subscription costs for the online platform and the costs of online consultations by the MHNP. Around one-third of participants in the i-Sleep group did not complete all sessions of the intervention. Therefore, the costs of online support provided by the MHNP were lower than anticipated at the start of the study. There was no statistical difference in total healthcare costs between the i-Sleep group and care-as-usual (mean difference €220; 95%CI −83 to 503). The largest contributor to the difference in total healthcare costs were costs of secondary care. Lost productivity costs in the two groups were relatively similar. However, informal care costs in the i-Sleep group were statistically significantly lower compared to the care-as-usual group (mean difference -€586; 95% CI −1735 to −14). The difference in total societal costs between the i-Sleep group and care-as-usual was not statistically significant (95%CI: −1282 to 645), but indicated that on average societal costs in the i-Sleep group were lower than in care-as-usual.

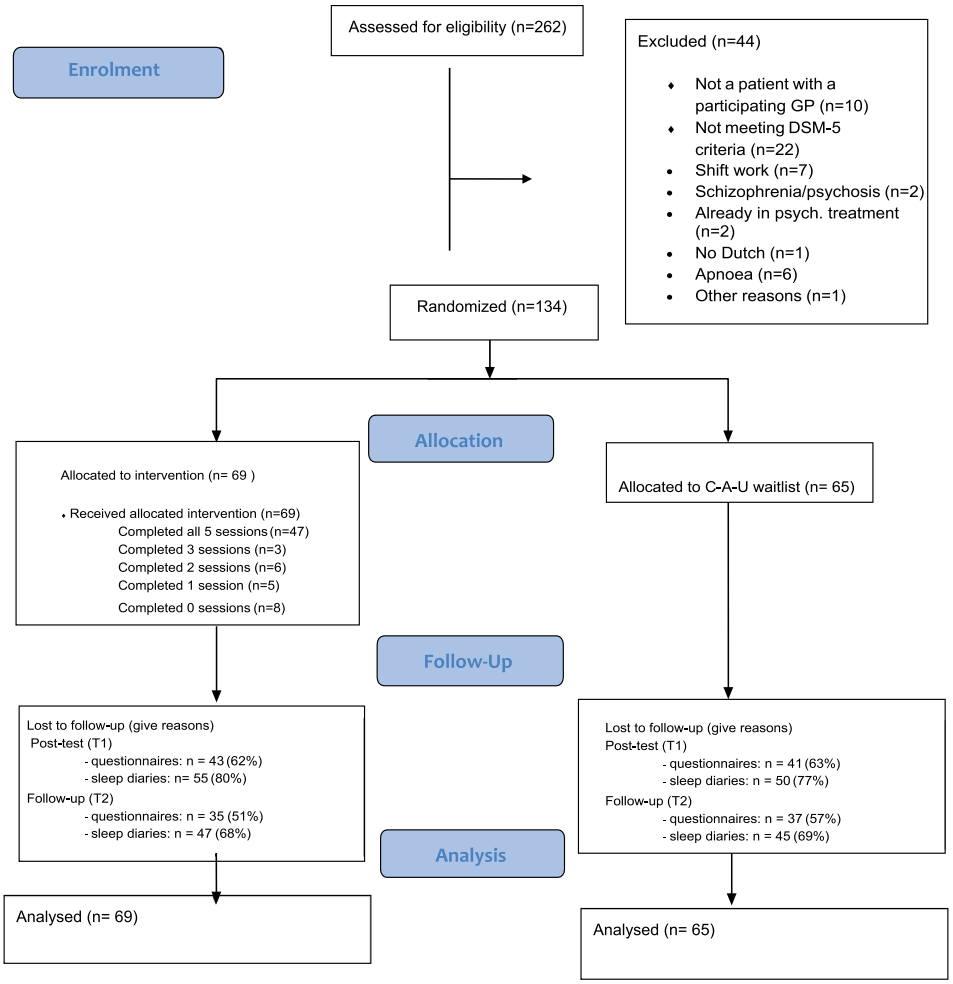

Figure 1. CONSORT flowchart of participant flow throughout the trial.

Cost-effectiveness and cost-utility

The results of the cost-effectiveness and cost-utility analyses are summarized in Table 3. For the continuous ISI score outcome at 26 weeks, the ICER was −81, meaning that 1 point improvement in insomnia severity score was associated with a saving of €81 for the i-Sleep as compared to the care-as-usual group. The CE plane for ISI score (Figure 2) shows that the statistical uncertainty surrounding the ICER is located in all four quadrants (Table 3) indicating considerable uncertainty. The majority of the bootstrapped cost-effect pairs (the gray dots) is gathered in the southeast quadrant, indicating that there is 59% probability for i-Sleep being more effective and less expensive compared to care-as-usual. The CEAC for ISI score (Figure 3) shows that if society is not willing to invest any money in the i-Sleep intervention, i.e. the ceiling ratio is 0 € per point of improvement in ISI score, the probability of i-Sleep being cost-effective in comparison with care-as-usual is 62%. At ceiling ratios of 250 and 450 € per point of improvement in ISI score the probability of i-Sleep being cost-effective compared to usual care is 87%, and 95%, respectively.

For the response outcome, the ICER was −1122 (see Table 3), indicating that 1 respondent with a clinically relevant response extra is associated with a saving of €1,122 in the i-Sleep group in comparison with the care-as-usual group. Approximately 60% of the bootstrapped cost-effect pairs are located in the southeast quadrant, confirming that i-Sleep is more effective and less expensive. At

Table 2. Multiply imputed pooled mean effects and costs (€2018) at 26 weeks (main analysis).

Outcome	i-Sleep group (n = 69)	Care-as-usual group (n = 65)	Adjusted Difference (95%CI)
Clinical effects (mean, [SE])			
Total ISI continuous score	12.6 (1.18)	16.8 (0.81)	3.9 (1.58; 6.26)[a]
Response to treatment	0.43 (0.090)	0.15 (0.058)	0.28 (0.13; 0.44)[a]
QALY	0.40 (0.009)	0.38 (0.011)	0.01 (−0.001; 0.02)[b]
Costs (€)			
Total healthcare costs	882 (145)	760 (166)	220 (−83; 503)[b]
Primary care	326 (51)	317 (47)	19 (−87; 128)[b]
Secondary care	555 (112)	442 (137)	201 (−51; 414)[b]
Medication	0.82 (0.37)	0.85 (0.41)	−0.15 (−1.4; 0.5)[b]
Intervention costs	99 (5)	0 (0)	98 (87; 107)[b]
Total lost productivity costs	2862 (769)	3731 (1191)	−622 (−2831; 1036)[b]
Absenteeism from paid work – Friction cost approach	1026 (438)	1015 (422)	179 (−750; 1260)[b]
Absenteeism from unpaid work	296 (91)	541 (179)	−178 (−562; 72)[b]
Presenteeism from paid work	882 (228)	1090 (545)	−38 (−1687; 573)[b]
Total other costs			
Informal care	228 (179)	828 (406)	−586 (−1735; −14)[b]
Total societal costs	3413 (588)	4234 (1085)	−318 (−1282; 645)[b]

[a]Adjusted for baseline ISI score and daytime consequences at baseline
[b]Adjusted for daytime consequences at baseline
ISI = Insomnia Severity Index; QALY = Quality-Adjusted Life-Year; SE = Standard Error; 95% CI = 95% Confidence Interval.

Table 3. Results of the multiply imputed cost-effectiveness and cost-utility analyses.

Outcome	ΔCosts (95%CI)	ΔEffects (95%CI)	ICER	Distribution on CE Plane			
				NE (%)	SE (%)	SW (%)	NW (%)
Main analysis							
Total ISI continuous score	−318 (−1282; 645)	3.91 (1.58; 6.26)	−81	40.6	59	0.1	0.3
Response to treatment	−318 (−1282; 645)	0.28 (0.13; 0.44)	−1122	40.7	59	0.1	0.2
QALY	−318 (−1282; 645)	0.01 (−0.001; 0.02)	− 28056	29	50	8	13
SA 1: Healthcare perspective							
Insomnia severity score	217 (−15; 449)	3.91 (1.58; 6.26)	55	88	12	0	0
Response to treatment	217 (−15; 449)	0.28 (0.13; 0.44)	764	88	12	0	0
QALY	217 (−15; 449)	0.01 (−0.001; 0.02)	20257	69	10	1	20
SA 2: Including only participants who completed i-Sleep							
Insomnia severity score	−489 (−1442; 464)	4.67 (2.5; 6.9)	−105	32	68	0	0
Response to treatment	−489 (−1442; 464)	0.34 (0.17; 0.50)	−1451	32	68	0	0
QALY	−489 (−1442; 464)	0.02 (0.006; 0.029)	−28361	27	63	4	6
SA 3: Human capital approach							
Insomnia severity score	−60 (−1438; 1319)	3.91 (1.58; 6.26)	−15	50	49	1	0
Response to treatment	−60 (−1438; 1319)	0.28 (0.13; 0.44)	−210	50	49	0	1
QALY	−60 (−1438; 1319)	0.01 (−0.001; 0.02)	−3910	37	43	6	14

QALY – Quality Adjusted Life Years; CE Plane – Cost-effectiveness plane; ICER – Incremental cost-effectiveness ratio; NE – Northeast; SE – Southeast; SW – Southwest; NW – Northwest; SA – Sensitivity analysis.

ceiling ratios of 0, 3,000 and 7,000 € per extra clinically relevant response, the probability that the i-Sleep intervention is cost-effective compared to care-as-usual is 61%, 84% and 95%, respectively. The CUA resulted in an ICER of −28,056, meaning that to gain 1 QALY €28,056 is saved with the i-Sleep intervention as compared to care-as-usual. The probability of the i-Sleep intervention being cost-effective compared to care-as-usual was 61%, 64%, and 67% at ceiling ratios of 0, 10,000 and 20,000 € per QALY gained, respectively.

Sensitivity analyses

The sensitivity analysis results are also presented in Table 3. In the analysis from the healthcare perspective (SA1), mean total costs were higher in the i-Sleep compared to the care-

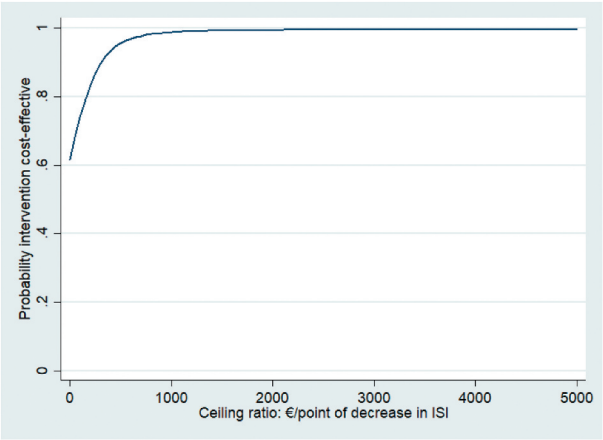

Figure 2. Cost-effectiveness plane for 1 extra point of improvement in ISI over 26 weeks (i-Sleep vs care-as-usual).

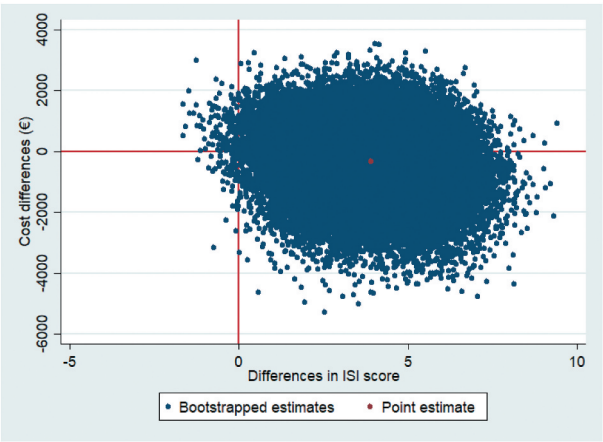

Figure 3. Cost-effectiveness acceptability curve for 1 extra point of improvement in ISI over 26 weeks (i-Sleep vs care-as-usual).

as-usual group (mean difference €217, 95%CI −15 to 449). At a ceiling ratio of 0 € per extra unit of effect, the probability of i-Sleep intervention being cost-effective compared to care-as-usual was 12% for the ISI score, clinically relevant response, and QALY outcomes. This increased to 95% for the ISI decrease and response outcomes at ceiling ratios of 200 and 3000 € per additional unit of effect, respectively. For the QALY outcome, the probability of i-Sleep intervention being cost-effective increased to 50% at a willingness-to-pay (WTP) ratio of 20,000 € per QALY gained.

The second sensitivity analysis included only participants who completed all five lessons of the i–Sleep intervention (68% of the total sample). A larger cost difference was found between groups as compared to the main analysis (mean difference -€489, 95%CI −1442 to 464). In addition, the mean pooled difference in QALYs became larger and was statistically significant (mean difference 0.02; 95%CI 0.006 to 0.03). The CEA curves indicated that the probability of i–Sleep being cost-effective was 67% at a ceiling ratio of 0 € per extra unit of effect for all outcomes. This probability increased to 95% at a WTP ratio of 5000 € per extra unit of effect for ISI score and 75% at a ceiling ratio of 20,000 €/QALY. In the final sensitivity analysis (SA3), results were similar to the main analysis.

Discussion

Main findings

This economic evaluation showed that the difference in societal costs between i-Sleep and care-as-usual was not statistically significant, although on average costs in the i-Sleep group were lower than in care-as-usual. Based on the CEA curves, we conclude that i-Sleep was cost-effective in comparison with care-as-usual both for the continuous ISI scores as for the percentage of participants with a clinically relevant response from a societal perspective. Although the point estimate of the ICER in the CUA indicates that i-Sleep was dominant over care-as-usual, there was considerable statistical uncertainty. Therefore, society should be willing to pay some money to reach acceptable probabilities of cost-effectiveness. Overall, sensitivity analyses showed similar results as the main analysis.

A clinically relevant improvement in insomnia severity symptoms was observed in the trial. These positive effects were not accompanied by a comparable effect on QALYs. It is possible that the EQ-5D-5 L that was used to calculate QALYs is not sensitive enough to detect changes in quality of life as a consequence of reduced insomnia symptoms. In a recent systematic review on the economic aspects related to CBT-I, the authors also concluded that the QALY might not be the most appropriate measurement to detect significant changes in insomnia symptoms related to treatment (Wickwire & Morin, 2020).

Evidence from a previous cost-effectiveness study comparing an internet-based CBT-I intervention with a waitlist control condition suggested that internet-delivered treatments have a higher probability of being cost-effective at relatively low willingness-to-pay ratios for treatment response than in our study (Thiart et al., 2016). Participants in this study were employees with work-related insomnia. Thus, the analysis was conducted from an employer's perspective, meaning that only lost productivity costs due to presenteeism and absenteeism from paid work were taken into account, whereas the current analysis was performed from a societal perspective. However, the most probable explanation for the difference between the two studies is that in the current study care-as-usual was used as a comparator. We hypothesize that because care-as-usual is an active treatment whereas waitlist control is not, differences in effects between the treatment groups are smaller than in Thiart et al. (2016).

Strengths and limitations

An important strength of the current study is the pragmatic design of the clinical trial, which enhances the generalizability of results to the average patient consulting their GP for sleep issues. Another strength is that we used the societal perspective, as recommended by the Dutch guidelines for economic evaluations, meaning that lost productivity costs are also included. Because insomnia has significant effects on work performance, this is an important strength of the study. Also, use of the societal perspective offered insight into potential shifting of costs between sectors. That is, costs might be incurred (or saved) in sectors other than the healthcare sector. As a result, an intervention might be cost-effective from the healthcare perspective, but not for the society as a whole. However, in order to use the societal perspective, it was necessary to use self-reported outcomes to measure healthcare utilization and productivity losses. This could potentially be a limitation of this study due to the occurrence of recall bias, although previous studies have shown that self-reported measures can be reliably used for recall periods up to 6 months (Van den Brink et al., 2005).

Another limitation was the rate of missing data (approximately 26%). Because total costs are a sum of the costs at the different time points, one missing observation already results in missing total cost estimations, which may explain the high rate of missing data. Multiple imputation was applied to account for the missing values, which is currently considered the most appropriate method to handle incomplete data in cost-effectiveness analyses (Burton et al., 2007). Additionally, the trial sample may not have been representative of the target population, with a higher percentage of respondents being white, female, and highly educated as compared to the general population. Finally, generalizability of

the findings might be limited by the fact that we used a convenience sample of general practices. It is not certain whether this sample adequately represents Dutch GPs. It is possible that participating practices were more involved in research in general, more engaged with new interventions, or more interested in sleep problems than other practices.

Implications

The i-Sleep intervention was considered cost-effective for insomnia severity symptoms when considering all patients, including those who did not finish the i-Sleep intervention (intention-to-treat analyses). When looking at completers only (67% of the sample), the effects on insomnia severity symptoms and QALYs were larger than in the main analysis, which resulted in higher probabilities of cost-effectiveness for i-Sleep. Further research is needed to identify strategies to increase adherence to internet-based mental health treatments even more, as this may increase cost-effectiveness as well.

Moreover, the recruitment process was not as productive as anticipated considering the number of participating GPs and MHNPs. A possible explanation for the slow inclusion could be that GPs often identify insomnia much less than expected given the prevalence rates (Bhaskar et al., 2016; Taylor et al., 2007). Insomnia is often comorbid with other mental and physical conditions. As a result, patients tend not to report insomnia-specific symptoms and, subsequently, GPs tend to focus less on treating insomnia. It is therefore possible that participating GPs did not always mention the trial during their insomnia-related consults. However, it should be stressed that referring patients as part of a clinical trial can be much more burdensome for healthcare professionals than in real-life practice, where treatment uptake would likely be enhanced. Additionally, as seen on the patient flow chart (Figure 1), considerably more patients were referred to than included in the trial, which suggests that GPs and nurses were not mainly responsible for the low inclusion rates. Patients have been reluctant to participate as well, possible because they were overwhelmed with health complaints and, as it is always the case in a RCT, wanted to avoid the 50% chance of receiving usual care. Future research should focus on GP awareness and involvement in the recruitment process as well as real-life uptake of i-Sleep treatment.

Improvement in insomnia severity symptoms was not linearly accompanied by increases in QALYs which is the primary outcome of interest for healthcare decision makers. Therefore, future research should be conducted to assess whether the EQ-5D (−5 L) is sensitive enough to pick up changes in quality of life as a consequence of decreased insomnia severity symptoms. Finally, healthcare costs and costs related to absenteeism from paid work were similar in both treatment groups. However, costs related to presenteeism, absenteeism from unpaid work and informal care were lower in the i-Sleep group than in the care-as-usual group. Although it is reasonable to assume that the reduction in costs associated with presenteeism and absenteeism from paid work are a direct result of the improvement in insomnia severity symptoms, this is less clear for informal care costs. This should be confirmed in future studies.

Conclusions

In conclusion, based on this economic evaluation the internet-delivered i-Sleep intervention may be considered cost-effective as compared to care-as-usual for patients with insomnia treated in general practice for insomnia severity symptoms from a societal perspective. However, the improvement in insomnia severity symptoms was not accompanied by substantial improvements in QALYs and therefore the intervention cannot be considered cost-effective for QALYs.

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Clinical trial registration

ID: NL5071 (NTR5202); trial name: (Cost-) effectiveness of a guided online CBT intervention in comparison to care-as-usual for patients with insomnia in general practice; URL: https://www.trialregister.nl/trial/5071

Disclosure statement

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Statement of significance

This is one of few studies to examine the cost-effectiveness of internet-delivered CBT for insomnia in the general practice. It is also the first cost-effectiveness study to take into consideration both the societal and healthcare perspectives, which yielded different results. Considering both costs and clinical effects simultaneously, internet-delivered CBT-I was found cost-effective as compared to care-as-usual with regards to clinical outcomes (insomnia severity scores). These findings are significant for decision makers given the high economic burden of insomnia and they show the potential of using internet-delivered CBT-I to address the lack of resources and expertise in treating insomnia symptoms. Further research is needed to improve adherence in internet-delivered CBT-I and better understand the relationship between insomnia and quality-of-life measurements.

References

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.

Andersson, G., Cuijpers, P., Carlbring, P., Riper, H., & Hedman, E. (2014). Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: A systematic review and meta-analysis. *World Psychiatry*, *13*(3), 288–295.https://doi.org/10.1002/wps.20151 . https://pubmed.ncbi.nlm.nih.gov/25273302/

Bastien, C. H., Vallieres, A., & Morin, C. M. (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Medicine*, *2*(4), 297–307. https://doi.org/10.1016/S1389-9457(00)00065-4

Bhaskar, S., Hemavathy, D., & Prasad, S. (2016). Prevalence of chronic insomnia in adult patients and its correlation with medical comorbidities. *Journal of Family Medicine and Primary Care*, *5*(4), 780–784. https://doi.org/10.4103/2249-4863.201153

Black, W. C. (1990). The CE plane: A graphic representation of cost-effectiveness. *Medical Decision Making*, *10*(3), 212–214. https://doi.org/10.1177/0272989X9001000308

Blom, K., Tarkian Tillgren, H., Wiklund, T., Danlycke, E., Forssen, M., Soderstrom, A., Johansson, R., Hesser, H., Jernelov, S., Lindefors, N., Andersson, G., & Kaldo, V. (2015). Internet-vs. group-delivered cognitive behavior therapy for insomnia: A randomized controlled non-inferiority trial. *Behaviour Research and Therapy*, *70*, 47–55. https://doi.org/10.1016/j.brat.2015.05.002

Bouwmans, C., De Jong, K., Timman, R., Zijlstra-Vlasveld, M., Van der Feltz-cornelis, C., Tan Swan, S., & Hakkaart-van Roijen, L. (2013). Feasibility, reliability and validity of a questionnaire on healthcare consumption and productivity loss in patients with a psychiatric disorder (TiC-P). *BMC Health Services Research*, *13*(1), 217. https://doi.org/10.1186/1472-6963-13-217

Burton, A., Billingham, L. J., & Bryan, S. (2007). Cost-effectiveness in clinical trials: Using multiple imputation to deal with incomplete cost data. *Clinical Trials: Journal of the Society for Clinical Trials*, *4*(2), 154–161. https://doi.org/10.1177/1740774507076914

Cheung, J. M. Y., Jarrin, D. C., Ballot, O., Bharwani, A. A., & Morin, C. M. (2019). A systematic review of cognitive behavioral therapy for insomnia implemented in primary care and community settings. *Sleep Medicine Reviews*, *44*, 23–36. https://doi.org/10.1016/j.smrv.2018.11.001

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Lawrence Erlbaum Associates.

Daley, M., Morin, C. M., LeBlanc, M., Gregoire, J. P., & Savard, J. (2009a). The economic burden of insomnia: Direct and indirect costs for individuals with insomnia syndrome, insomnia symptoms, and good sleepers. *Sleep*, *32*(1), 55–64. https://pubmed.ncbi.nlm.nih.gov/19189779/

Daley, M., Morin, C. M., LeBlanc, M., Gregoire, J. P., Savard, J., & Baillargeon, L. (2009b). Insomnia and its relationship to health-care utilization, work absenteeism, productivity and accidents. *Sleep Medicine*, *10*(4), 427–438. https://doi.org/10.1016/j.sleep.2008.04.005

De Bruin, E. J., Van Steensel, F. J., & Meijer, A. M. (2016). Cost-effectiveness of group and internet cognitive behavioral therapy for insomnia in adolescents: Results from a randomized controlled trial. *Sleep*, *39*(8), 1571–1581. https://doi.org/10.5665/sleep.6024

Edinger, J. D., & Means, M. K. (2005). Cognitive-behavioral therapy for primary insomnia. *Clinical Psychology Review*, *25*(5), 539–558. https://doi.org/10.1016/j.cpr.2005.04.003

Edinger, J. D., & Wohlgemuth, W. K. (1999). The significance and management of persistent primary insomnia: The past, present and future of behavioral insomnia therapies. *Sleep Medicine Reviews*, *3*(2), 101–118. https://doi.org/10.1016/S1087-0792(99)90018-7

Efron, B. (1994). Missing data, imputation, and the bootstrap. *Journal of the American Statistical Association*, *89*(426), 463–475. https://doi.org/10.1080/01621459.1994.10476768

Espie, C. A. (2006). *Overcoming insomnia and sleep problems: A self-help guide using cognitive behavioral techniques*. Robinson.

Espie, C. A., Emsley, R., Kyle, S. D., Gordon, C., Drake, C. L., Siriwardena, A. N., Cape, J., Ong, J. C., Sheaves, B., Foster, R., Freeman, D., Costa-Font, J., Marsden, A., & Luik, A. I. (2019). Effect of digital cognitive behavioral therapy for insomnia on health, psychological well-being, and sleep-related quality of life: A randomized clinical trial. *JAMA Psychiatry*, *76*(1), 21–30. https://doi.org/10.1001/jamapsychiatry.2018.2745

Espie, C. A., Kyle, S. D., Williams, C., Ong, J. C., Douglas, N. J., Hames, P., & Brown, J. S. (2012). A randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. *Sleep*, *35*(6), 769–781. https://doi.org/10.5665/sleep.1872

Everitt, H., McDermott, L., Leydon, G., Yules, H., Baldwin, D., & Little, P. (2014). GPs' management strategies for patients with insomnia: A survey and qualitative interview study. *British Journal of General Practice*, *64*(619), e112–119. https://doi.org/10.3399/bjgp14X677176

Faria, R., Gomes, M., Epstein, D., & White, I. R. (2014). A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *Pharmacoeconomics*, *32*(12), 1157–1170. https://doi.org/10.1007/s40273-014-0193-3

Fenwick, E., O'Brien, B. J., & Briggs, A. (2004). Cost-effectiveness acceptability curves–facts, fallacies and frequently asked questions. *Health Economics*, *13*(5), 405–415. https://doi.org/10.1002/hec.903

Hakkaart-van Roijen, L., Van Der Linden, N., Bouwmans, C., Kanters, T., & Tan, S. S. (2015). *Handleiding voor kostenonderzoek: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg*. Zoorginstituut Nederland.

Hakkaart-van Roijen, L., Van Straten, A., Donker, M., & Tiemens, B. (2002). *Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (Tic-P)*. Institute for Medical Technology Assessment: Erasmus Universiteit Rotterdam.

Herdman, M., Gudex, C., Lloyd, A., Janssen, M., Kind, P., Parkin, D., Bonsel, G., & Badia, X. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research*, *20*(10), 1727–1736. https://doi.org/10.1007/s11136-011-9903-x

Horsch, C., Lancee, J., Beun, R. J., Neerincx, M. A., & Brinkman, W. P. (2015). Adherence to technology-mediated insomnia treatment: A meta-analysis, interviews, and focus groups. *Journal of Medical Internet Research*, *17*(9), e214. https://doi.org/10.2196/jmir.4115

Lancee, J., Van den Bout, J., Sorbi, M. J., & Van Straten, A. (2013). Motivational support provided via email improves the effectiveness of internet-delivered self-help treatment for insomnia: A randomized trial. *Behaviour Research and Therapy*, *51*(12), 797–805. https://doi.org/10.1016/j.brat.2013.09.004

Lancee, J., Van den Bout, J., Van Straten, A., & Spoormaker, V. I. (2012). Internet-delivered or mailed self-help treatment for insomnia? A randomized waiting-list controlled trial. *Behaviour Research and Therapy*, *50*(1), 22–29. https://doi.org/10.1016/j.brat.2011.09.012

Lancee, J., Van Straten, A., Morina, N., Kaldo, V., & Kamphuis, J. H. (2016). Guided online or face-to-face cognitive behavioral treatment for insomnia: A randomized wait-list controlled trial. *Sleep*, *39*(1), 183–191. https://doi.org/10.5665/sleep.5344

Li, M. J., Kechter, A., Olmstead, R. E., Irwin, M. R., & Black, D. S. (2018). Sleep and mood in older adults: Coinciding changes in insomnia and depression symptoms. *International Psychogeriatrics*, *30*(3), 431–435. https://doi.org/10.1017/S1041610217001454

Morin, C. M., Belleville, G., Belanger, L., & Ivers, H. (2011). The insomnia severity index: Psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep*, *34*(5), 601–608. https://doi.org/10.1093/sleep/34.5.601

Morin, C. M., & Espie, C. A. (2003). *Insomnia: A clinical guide to assessment and treatment*. Kluwer Academic/Plenum Publishers.

Morin, C. M., LeBlanc, M., Daley, M., Gregoire, J. P., & Merette, C. (2006). Epidemiology of insomnia: Prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors. *Sleep Medicine*, *7*(2), 123–130. https://doi.org/10.1016/j.sleep.2005.08.008

The National Institute for Health and Care Excellence [NICE]. (2004). *Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia*. NICE. Technology Appraisal Guidance [TA77].

NHG-werkgroep Slaapproblemen en slaapmiddelen. NHG-Standaard Slaapproblemen en slaapmiddelen (tweede herziening). Huisarts Wet. 2014; 57(7), 352-61, 57(7), 352-61.

Olfson, M., Wall, M., Liu, S. M., Morin, C. M., & Blanco, C. (2018). Insomnia and impaired quality of life in the United States. *The Journal of Clinical Psychiatry*, *79*(5). https://doi.org/10.4088/JCP.17m12020

Qaseem, A., Kansagara, D., Forciea, M. A., Cooke, M., Denberg, T. D., & Clinical Guidelines Committee of the American College of Physicians. (2016). Management of chronic insomnia disorder in adults: A clinical practice guideline from the American College of Physicians. *Annals of Internal Medicine*, *165*(2), 125–133. https://doi.org/10.7326/M15-2175

Riemann, D., Baglioni, C., Bassetti, C., Bjorvatn, B., Dolenc Groselj, L., Ellis, J. G., Espie, C. A., Garcia-Borreguero, D., Gjerstad, M., Goncalves, M., Hertenstein, E., Jansson-Frojmark, M., Jennum, P. J., Leger, D., Nissen, C., Parrino, L., Paunio, T., Pevernagie, D., Verbraecken, J., Weess, H. G., … Spiegelhalder, K. (2017). European guideline for the diagnosis and treatment of insomnia. *Journal of Sleep Research*, *26*(6), 675–700.https://doi.org/10.1111/jsr.12594 . https://pubmed.ncbi.nlm.nih.gov/28875581/

Rubin, D. B. (1987). *Multiple imputation for nonresponse in surveys*. Wiley.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry*, *59 Suppl 20*, 22–33;quiz 34–57. https://pubmed.ncbi.nlm.nih.gov/9881538/

Sofi, F., Cesari, F., Casini, A., Macchi, C., Abbate, R., & Gensini, G. F. (2014). Insomnia and risk of cardiovascular disease: A meta-analysis. *European Journal of Preventive Cardiology*, *21*(1), 57–64.https://doi.org/10.1177/2047487312460020 . https://pubmed.ncbi.nlm.nih.gov/22942213/

Statline Netherlands. (2020). *Consumer Price Index*.Statistics Netherlands' database.

Taylor, D. J., Mallory, L. J., Lichstein, K. L., Durrence, H. H., Riedel, B. W., & Bush, A. J. (2007). Comorbidity of chronic insomnia with medical problems. *Sleep*, *30*(2), 213–218. https://doi.org/10.1093/sleep/30.2.213

Thiart, H., Ebert, D. D., Lehr, D., Nobis, S., Buntrock, C., Berking, M., Smit, F., & Riper, H. (2016). Internet-based cognitive behavioral therapy for insomnia: A health economic evaluation. *Sleep*, *39*(10), 1769–1778.https://doi.org/10.5665/sleep.6152 . https://pubmed.ncbi.nlm.nih.gov/27450686/

Thorndike, F. P., Ritterband, L. M., Saylor, D. K., Magee, J. C., Gonder-Frederick, L. A., & Morin, C. M. (2011). Validation of the insomnia severity index as a web-based measure. *Behavioral Sleep Medicine*, *9*(4), 216–223. https://doi.org/10.1080/15402002.2011.606766

Van Ballegooijen, W., Cuijpers, P., Van Straten, A., Karyotaki, E., Andersson, G., Smit, J. H., & Riper, H. (2014). Adherence to Internet-based and face-to-face cognitive behavioural therapy for depression: A meta-analysis. *PLoS One*, *9*(7), e100674. https://doi.org/10.1371/journal.pone.0100674

Van Buuren, S., & Groothuis-Oudshoorn, K. (2011). mice: Multivariate imputation by chained equations in R. *Journal of Statistical Software*, *45*(67). https://doi.org/10.18637/jss.v045.i01

Van den Brink, M., Van den Hout, W. B., Stiggelbout, A. M., Putter, H., Van de Velde, C. J., & Kievit, J. (2005). Self-reports of health-care utilization: Diary or questionnaire? *International Journal of Technology Assessment in Health Care*, *21*(3), 298–304. https://doi.org/10.1017/s0266462305050397 . https://pubmed.ncbi.nlm.nih.gov/16110708/

Van den Hout, W. B. (2010). The value of productivity: Human-capital versus friction-cost method. *Annals of the Rheumatic Diseases*, *69 Suppl 1*, i89–91. https://doi.org/10.1136/ard.2009.117150

Van der Zweerde, T., Lancee, J., Slottje, P., Bosmans, J., Van Someren, E., Reynolds, C., 3rd, Cuijpers, P., & Van Straten, A. (2016). Cost-effectiveness of i-Sleep, a guided online CBT intervention, for patients with insomnia in general practice: Protocol of a pragmatic randomized controlled trial. *BMC Psychiatry*, *16*(1), 85. https://doi.org/10.1186/s12888-016-0783-z

Van Der Zweerde, T., Lancee, J., Slottje, P., Bosmans, J. E., Van Someren, E. J. W., & Van Straten, A. (2020). Nurse-guided internet-delivered cognitive behavioral therapy for insomnia in general practice: Results from a pragmatic randomized clinical trial. *Psychotherapy and Psychosomatics*, *89*(3), 174–184. https://doi.org/10.1159/000505600

Van Straten, A., Van der Zweerde, T., Kleiboer, A., Cuijpers, P., Morin, C. M., & Lancee, J. (2018). Cognitive and behavioral therapies in the treatment of insomnia: A meta-analysis. *Sleep Medicine Reviews*, *38*, 3–16. https://doi.org/10.1016/j.smrv.2017.02.001

Verbeek, I., & Klip, E. (2005). *Insomnia*. Boom Uitgevers.

Versteegh, M. M., Vermeulen, K. M., Evers, S. M., De Wit, G. A., Prenger, R., & Stolk, E. A. (2016). Dutch tariff for the five-level version of EQ-5D. *Value in Health*, *19*(4), 343–352. https://doi.org/10.1016/j.jval.2016.01.003

White, I. R., Royston, P., & Wood, A. M. (2011). Multiple imputation using chained equations: Issues and guidance for practice. *Statistics in Medicine*, *30*(4), 377–399. https://doi.org/10.1002/sim.4067

Wickwire, E. M., & Morin, C. M. (2020). Advancing a value framework for sleep: Update on economic aspects of cognitive-behavioral treatments for insomnia. *Sleep Medicine Reviews*, *54*, 101387. https://doi.org/10.1016/j.smrv.2020.101387 . https://pubmed.ncbi.nlm.nih.gov/33007737/

Willan, A. R., Briggs, A. H., & Hoch, J. S. (2004). Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. *Health Economics*, *13*(5), 461–475. https://doi.org/10.1002/hec.843

Wittchen, H. U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jonsson, B., Olesen, J., Allgulander, C., Alonso, J., Faravelli, C., Fratiglioni, L., Jennum, P., Lieb, R., Maercker, A., Van Os, J., Preisig, M., Salvador-Carulla, L., Simon, R., & Steinhausen, H. C. (2011). The size and burden of mental disorders and other disorders of the brain in Europe 2010. *European Neuropsychopharmacology*, *21*(9), 655–679. https://doi.org/10.1016/j.euroneuro.2011.07.018