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Cost-effectiveness and cost-utility of exposure-based vs. traditional cognitive behavior therapy for fibromyalgia: Results from a randomized controlled trial

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ABSTRACT

Fibromyalgia (FM) is associated with significant economic costs. Given the limited availability of effective and accessible treatments, it is crucial to develop and assess the cost-effectiveness of new interventions. This study aimed to evaluate the cost-effectiveness of online exposure therapy (EXP-CBT) versus online traditional CBT (T-CBT) for FM. We analyzed health economic data from a randomized controlled trial in which 274 participants with FM were assigned to either EXP-CBT or T-CBT. The time horizon was 15 months, and treatment effectiveness relative to costs was evaluated from both a societal perspective (direct and indirect costs) and a health care perspective (direct medical costs only). Bootstrapped net benefit regression analyses were conducted to compare cost and effect differences between EXP-CBT and T-CBT under various willingness-to-pay scenarios. The results showed that the incremental cost-effectiveness ratio was −1477/0.09 = –$16,884 from the societal perspective, indicating that EXP-CBT was cost-effective. Each additional successfully treated case (treatment responder) in EXP-CBT compared to T-CBT was associated with lower costs and there was a 69% probability of EXP-CBT being cost-effective even at a willingness-to-pay threshold of $0. The cost-utility analysis resulted in an estimate of −1477/0.05 = –$28,763, also here with an 69% probability of EXP-CBT being cost-effective at a willingness-to-pay threshold of $0. There were no significant differences in total costs or effectiveness between EXP-CBT and T-CBT. In conclusion, online exposure therapy may be a cost-effective alternative to online traditional CBT, but there appears to be no marked cost- or effect differences between the two treatments.
Perspective: This article presents a cost-effectiveness evaluation of online exposure therapy compared to online traditional CBT for fibromyalgia. Results indicate that online exposure therapy may be cost-effective compared to online traditional CBT. However, as there were no marked cost- or effect differences between the treatments, results should be interpreted with caution.

Introduction

The common and disabling disorder fibromyalgia (FM)[1,2] is — perhaps more than any other chronic pain condition — associated with tremendous costs both for health care and for society as a whole.[3] This has been shown in several well-controlled studies,[4–8] and excess FM-related costs include both direct medical costs (e.g., health care visits and medications) and indirect costs such as sick leave, work loss and unemployment. There is some indication that fibromyalgia is one of the pain conditions with the highest rates of sick leave, unemployment, claims for incapacity benefits, work absenteeism, and per-patient costs.[9] Against this background, cost-effectiveness analyses (CEA) of interventions for FM are crucial.

In a CEA, the effect of a given intervention is analyzed in relation to

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its associated costs. This is normally done by estimating the cost difference between the treatment and a control condition, and subsequently dividing this estimate by the net clinical effect (e.g., difference in responder/remission status). The result can provide decision makers with data on what treatments give the maximum treatment output, taking both costs and effects into consideration (i.e., what gives the most "bang for the buck").[10] There is still no curative treatment for FM and current treatment approaches therefore aim to enhance patient functioning and alleviate symptoms if possible. Cognitive behavior therapy (CBT) has shown small effects in improving symptoms and function,[11] however, this help is not available for many patients with FM. Hence, there is a need to develop effective and accessible treatments that hopefully also lead to reduced societal costs.

Exposure therapy is a variant of CBT that has been found to be effective for various chronic pain-related conditions.[12–17] Our research group has previously found that online exposure therapy results in large between-group effect sizes when compared to a waitlist control group.[18] A subsequent CEA demonstrated that the treatment was highly cost-effective compared to waitlist, with a 100% probability of being cost-effective even with a willingness-to-pay value of $0.[19] As a next step, a large-scale single-blinded randomized controlled trial was recently performed where exposure therapy (EXP-CBT) was compared to traditional CBT (T-CBT), which is the most evaluated psychological treatment for FM. Both treatments were provided online, which may increase treatment availability[20,21] as online CBT often requires less than 20% of the therapist time in face-to-face CBT, thus having the potential to increase treatment capacity and of being cost-effective compared to face-to-face treatment.[22] The results of the trial showed no significant between-group difference on FM severity, but both treatments demonstrated moderate to large (d = 0.77–0.87) within-group effects.[23]

The aim of the current study was to compare the cost-effectiveness of EXP-CBT to T-CBT using data from the above-mentioned randomized controlled trial. Analyses were conducted both from a societal perspective — including both direct costs related to medical resource utilization and indirect costs attributable to production losses such as sick leave and work cutback — and from a health care provider perspective including costs of medical resource utilization only.

Methods

Trial design

This cost-effectiveness study was based on health economic data collected as part of a previously reported single-blinded randomized controlled trial,[23] in which 274 adult participants with FM were randomized 1:1 to either online exposure therapy (EXP-CBT) or online traditional CBT (T-CBT). The data used in this analysis was collected online at pre-treatment, post-treatment (10 weeks after pre-treatment assessment), and at follow-up 15 months after the pre-treatment assessment (15MFU). The time horizon was the whole study period, i.e., 15 months. Study sites were Karolinska Institutet, Stockholm, Sweden, and Uppsala University, Uppsala, Sweden. The study was approved by the Swedish Ethical Review Authority (2021–03302) and registered at ClinicalTrials.gov (registration ID: NCT05058911). Results are reported in accordance with Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement.[24] All subjects provided informed consent.

Participants

Participants were self-referred through the study website, and the trial was advertised primarily through social media, national newspapers, patient organizations, and recruitment posters. To be eligible for the trial, participants were required to (1) be at least 18 years old, (2) be residing in Sweden, (3) confirm having received a diagnosis of FM from a physician and (4) have continuous access to a computer, smartphone, or tablet with continuous internet access. Concurrent use of psychotropic medication was allowed if doses had been held stable for at least 4 weeks prior to randomization and the participant agreed to keep it constant during the 10 weeks of treatment. Exclusion criteria were (1) severe depression, as indicated by $\geq$ 30 on the Montgomery Åsberg Depression Rating Scale – Self Rated (MADRS-S[25]), (2) suicidal ideation, indicated by $\geq$ 4 on the suicidal ideation item on MADRS-S, (3) psychosis, (4) ongoing alcohol or substance use disorder likely to severely interfere with treatment, (5) concurrent psychological treatment, (6) pregnancy beyond 29 weeks' gestation, (7) a medical condition other than FM that required immediate treatment or was considered the participant's primary condition, and (8) insufficient computer- or language skills to manage a text-based treatment. Demographic and clinical characteristics are shown in Table 1.

Involvement of participants and patient representatives

The EXP-CBT protocol has been continuously developed based on feedback from participants in previous trials.[18,26] The Swedish Fibromyalgia Association was informed about the study and contributed to the recruitment process by sharing details on their website. Social media recruitment advertisements were tailored to target individuals of both sexes and with a diversity in age.

Interventions

Common treatment features

Treatments were 10 weeks long and delivered as therapist-guided online treatment, which is a widely evaluated treatment format.[27] Participants were instructed to regularly log in to a secure (encrypted traffic, two-factor authentication) online treatment platform and work with the treatment material, which was conveyed via illustrated self-help text divided into 8 interactive modules. The modules contained psychoeducational material, instructions for exercises, worksheets, and homework assignments, all of which could also be downloaded as audio files. Participants had gradual access to the modules after having reported to their therapist and completed homework assignments. Treatments were about equally long, were about equally easy to read, and included about the same number of illustrations. The trial was designed to ensure that both therapies were delivered by allegiant therapists, that therapists were supervised regularly by experts, and with minimal risk of cross-contamination. EXP-CBT was delivered at Karolinska Institutet and T-CBT was delivered at Uppsala University. Prior to the study start all therapists received a joint introduction to the treatment platform and internet-delivered treatment, as well as a specific go-through of the respective treatment protocol with the respective authors (M.H-L. and M.B., respectively). During the trial therapists attended weekly group supervision with the author of the respective treatment manual, where the focus was to foster allegiance and promote adherence to the treatment manual. Therapists were licensed psychologists or students in the final year of their master-level clinical psychology program, and the work groups at each site were matched for competence and experience. The main role of the therapist was to provide support for treatment progress through positive reinforcement, address any questions that might arise, and to assist the participant in applying the treatment model to their own FM problems. All therapists received a written guide including a Q&A for the respective treatments, and examples of written communication, to facilitate learning and model expected therapist behavior. Communication with the therapist took place via email-like messages, where the participant could expect a response within two working days. Participants were also telephoned for the purpose of problem-solving around treatment inactivity and sometimes for clarifying treatment instructions and providing technical support. Participants who had been inactive for three days were contacted by their therapist via SMS or telephone.

Table 1
Demographic and clinical characteristics of participants randomized to online exposure-based cognitive behavior therapy (EXP-CBT) or online traditional cognitive behavior therapy (T-CBT) for fibromyalgia and included in the complete case analysis (CCA) as well as for the full sample.

	EXP-CBT CCA (n = 118)	EXP-CBT full sample (n = 137)	T-CBT CCA (n = 115)	T-CBT full sample (n = 137)	Total in CCA analysis (n = 233)	Total (N = 274)
Sociodemographic variables						
Mean (SD) age in years, range	51 (11), 28–76	50 (12), 21–76	52 (11), 23–76	52 (11), 18–76	51 (11) 23–76	51 (11), 18–76
Women	116 (98%)	135 (99%)	112 (97%)	134 (98%)	228 (98%)	269 (98%)
Educational attainment						
Compulsory school (≤9 years)	5 (4%)	9 (7%)	8 (7%)	10 (7%)	13 (6%)	19 (7%)
Upper secondary school (≤3 years)	32 (27%)	39 (28%)	34 (30%	41 (30%)	66 (28%	80 (29%)
Post-secondary or university	81 (69%)	89 (65%)	73 (63%)	86 (63%)	154 (66%)	175 (64%)
Married or de facto	93 (79%)	103 (75%)	89 (77%)	103 (75%)	182 (78%)	206 (75%)
Occupational status						
Working full or part time	75 (64%)	83 (61%)	71 (62%)	86 (63%)	146(63%)	169 (62%)
Retired	24 (20%)	24 (18%)	21 (18%)	22 (16%)	45 (19%)	46 (17%)
Disability pension	5 (4%)	8 (6%)	9 (8%)	11 (8%)	14 (6%)	18 (7%)
Unemployed	4 (3%)	7 (5%)	4 (3%)	7 (5%)	8 (3%)	14 (5%)
Student	5 (4%)	6 (4%)	5 (4%)	7 (5%)	10 (4%)	13 (5%)
On sick leave	3 (3%)	6 (4%)	5 (4%)	2 (1%)	8 (3%)	8 (3%)
Other or unclear	2 (2%)	4 (3%)	0	3 (2%)	2 (1%)	7 (3%)
Clinical variables						
Fibromyalgia						
Mean (SD) years with diagnosis, range	11 (8),1–31	10 (9), 0–44	12 (9), 0–36	11 (9), 0–35	11 (8), 0–36	11 (9), 0–44
Overall symptom severity						
Mild (FIQ<39)	15 (13%)	15 (11%)	8 (7%)	8 (6%)	23 (10%)	23 (8%)
Moderate (39≤FIQ<59)	47 (40%)	57 (42%)	45 (39%)	55 (40%)	92 (39%)	112 (41%)
Severe (FIQ≥59)	56 (47%)	65 (47%)	62 (54%)	74 (54%)	118 (51%)	139 (51%)
At least one comorbid somatic condition*	82 (69%)	94 (69%)	86 (75%)	103 (75%)	168 (72%)	197 (72%)

FIQ = Fibromyalgia Impact Questionnaire, range 0-100. Post-secondary or university = International Standard Classification of Education (ISCED) 1997 level 4 or higher. *As reported by the patient in response to the questionnaire item "Do you have any physical illness over and above fibromyalgia?"

Online exposure therapy (EXP-CBT)

Exposure therapy was carried out in accordance with the previously evaluated protocol.[18] Treatment interventions comprised psychoeducation about FM and pain, exposure to stimuli associated with FM symptoms and FM-related distress, and training in mindful attention exercises to facilitate exposure. Exposure exercises were based on (1) approaching situations, activities, and stimuli previously avoided (e.g., planning a social activity and participating in it regardless of symptom level, doing leisure- or sports activities, or intentional observation and labelling of physical sensations and symptoms), and (2) response prevention, i.e., refraining from avoidance behaviors (e.g., using short-term pain medication, resting contingent on symptom level), including covert behaviors such as distraction and monitoring of symptoms. The total mean therapist time was 203 min (SD = 202) and the average number of modules completed was 5.8 (SD = 2.4) out of 8.

Online traditional CBT (T-CBT)

Traditional CBT was carried out in accordance with a protocol that had previously been evaluated for chronic pain,[28] with small changes primarily in the first module to ensure that both treatments began with identical psychoeducational texts about FM and pain, including the complexity of the pain experience and that pain does not always equal damage. Treatment interventions consisted of relaxation training, activity scheduling, stress management, cognitive restructuring techniques, sleep-promoting techniques, physical activity, and pacing (balancing activity and rest). Participants were instructed to work continuously with activity scheduling and to make use of the other components before, during, and after activities, to manage pain and pain-related distress. The total mean therapist time was 171 min (SD = 125), with an average number of modules completed of 6.0 (SD = 2.5).

Cost-data assessments

Health economic data was obtained at pre-treatment, post-treatment and at 15 months after pre-treatment assessment (i.e., 15-month follow-up, 15MFU), using the Trimbos and Institute of Medical Technology Assessment Cost Questionnaire for Psychiatry (TIC-P[29]), a cost diary extensively used in studies of cost-of-illness (e.g.,[30,31] and cost-effectiveness (e.g.,[32–34]). The TIC-P questionnaire assesses participants' direct medical costs (i.e., health care consumption and use of medication) and productivity loss (i.e., unemployment, sick leave, work loss and domestic loss). Participants provide information on their formal health care utilization (e.g., visits to a general practitioner or specialist physicians), use of medication, and time spent in informal health-enhancing activities (e.g., engagement in activities such as massage- or spa therapy). TIC-P also measures days of sick leave and reduced work capacity, both at work and in their free time. All questions concern the last month, except for medication use that refer to the last two weeks. TIC-P has been shown to have satisfactory construct validity regarding contacts with psychotherapist and long-term work absence, and to be feasible and reliable for collecting data on medical consumption and productivity losses.[35]

Monetary losses related to sick leave, reduced work productivity, and household cutbacks were estimated by considering the average gross earnings in Sweden, based on the participants' level of education.[36] Medical costs were determined using published national tariffs for health care services in Sweden while expenses associated with informal health-enhancing activities and products including supplements were calculated based on the Swedish prevailing market prices. Costs for medications were determined using the database from the Dental and Pharmaceutical Benefits Agency in Sweden and calculated based on the individual dosage and number of doses taken per 14 days. Domestic loss hourly tariff was based on the post-tax wage per hour in Sweden and estimated to $17.06.[37] Treatment costs for online exposure therapy and traditional CBT were calculated based on the cost for the therapist time, which was estimated to $218 per hour using the mean between the full economic cost price of a licensed clinical psychologist employed in primary care and in outpatient psychiatry. This cost was multiplied by

the total therapist time spent on each participant, including time spent on telephone calls. All costs were initially assessed in Swedish Krona (SEK) and converted into US Dollar ($) using 2022 as the reference year (yielding a SEK1 equivalent of US$0.0988) and expressed as estimated accumulated total costs over the 15-month period.

Clinical outcome assessments

The primary measure of treatment effectiveness, defined as treatment responder, was assessed using the Fibromyalgia Impact Questionnaire (FIQ[38]). The FIQ is a composite measure of the overall severity of fibromyalgia in terms of pain, fatigue, sleepiness, mood disturbance, and impact on daily life (disability). It is a validated and disease-specific instrument that is known to be reliable and sensitive to change.[39] The secondary clinical outcome, defined as quality-adjusted life years (QALYs), was assessed using the 5-level EuroQol questionnaire (ED-5Q[40]). EQ-5D is a non-disease specific questionnaire aiming to measure quality of life in five health domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, yielding a utility score for the cost-utility analysis.

Statistical analyses

Treatment effectiveness was analyzed using mixed effects linear regression models. Responder status was determined using the established criterion for minimal clinically important change, defined as a 14% reduction in the FIQ score[41] at the 15-month follow-up. Standardized effect sizes were reported as Cohen's *d* based on pooled standard deviations.[42] Logistic regression was employed to explore potential dose-response relationships between minimally clinically important change (see above) and total costs.

Accumulated total costs were estimated using linear interpolation, to estimate costs between the three time points (pre-treatment, post-treatment and 15MFU, respectively), and area under the curve calculation to estimate the total cost for the whole study period (i.e., the cost from the pre- to post-treatment, plus the cost from post-treatment to 15MFU). This method accounts for changes over time and is thereby able to capture trends, which is favorable when evaluating the effects of an intervention compared to just multiplying observed monthly costs with the time horizon (e.g., 15 months). Cost-effectiveness and cost-utility analyses were conducted as complete case analyses, meaning only participants that provided data on all three time points were included.

The study employed two approaches to evaluate the cost-effectiveness of EXP-CBT vs. T-CBT. First, the incremental cost-effectiveness ratio (ICER) was calculated. The ICER represents the cost difference associated with achieving one additional successful treatment outcome (responder) in the EXP-CBT group compared to the T-CBT group. In essence, it quantifies the net cost of achieving one additional positive response when providing an experimental condition (i.e., EXP-CBT) compared to a control condition (i.e., T-CBT). The ICER was estimated by dividing the difference in estimated accumulated costs between EXP-CBT and T-CBT during the 15-month period with the difference in the average effectiveness (i.e., in this study difference in responder rates at 15MFU) of the two conditions.[10] Recognizing that cost-effectiveness is not absolute but depends on societal values, the study also assessed cost-effectiveness in relation to varying levels of societal willingness-to-pay using the net benefit approach. This analysis explored the cost-effectiveness of the interventions by considering different thresholds of what society deems acceptable to spend for achieving one additional unit of improvement.[10] The net benefit for each participant was determined using the formula (λ x E) - ΔC, where λ represents the willingness to pay (i.e., various amounts society is willing to invest for an additional unit of improvement), E denotes efficacy (in this case, either responder status or QALYs gained), and ΔC stands for the accumulated costs from pre-treatment to the 15MFU[10]. Individual net benefits were calculated by applying different values of λ and by fitting regression models under non-parametric bootstrapping (5000 replications) to estimate the differences between EXP-CBT and T-CBT. The results are illustrated using an acceptability curve, which demonstrates the probability of the treatment being cost-effective at various willingness-to-pay values.

Cost-utility analysis was carried out following the guidelines of the EuroQol Group. This analysis was identical to the cost-effectiveness evaluation described earlier, but utilized a generic measure—QALYs gained, as assessed by the EQ-5D—instead of a symptom-specific outcome. Given that the cost data were expected to be non-normally distributed, *p*-values for both analyses were derived through a general linear model combined with non-parametric bootstrapping (5000 iterations), which is considered effective in providing reliable estimates of cost standard errors. In addition to analyzing cost-effectiveness from a health-care provider perspective, where only the direct medical costs are included, the analyses were also conducted from a societal perspective, including all direct and indirect costs. This gives an estimation of the total cost-effectiveness of EXP-CBT involving all available payers (i.e., the patient, the employer, the health-care system, and society). All analyses were conducted in Stata/IC 16[43] and Microsoft Excel 16.

Results

Data loss

For the clinical outcome measure FIQ, 100% of the data was obtained at pre-treatment and 86% at the 15-month follow-up ($N = 235$). On the health-economic measures, 100% of the data was obtained at pre-treatment, 95% at post-treatment, and 86% at 15MFU (235 out of 274 participants), with 233 participants providing data for all three assessment points (85%). Due to the relatively low degree of missing data, that data was deemed to be missing at random and the fact that the missing data was evenly distributed between the two groups (EXP-CBT 86%; T-CBT 84%), no imputation of data was deemed necessary.

Clinical efficacy

The mean score on the FIQ at pre-treatment was 56.9 (SD = 14.8) for the EXP-CBT group and 60.0 (SD = 12.0) for the T-CBT group. Corresponding figures at 15MFU were 43.8 (SD = 19.8) and 48.7 (SD = 18.8), respectively. There were 59% responders in the EXP-CBT group at 15MFU, compared to 50% in the T-CBT group. The difference in the mean response was non-significant when analyzed in a bootstrapped linear regression model (estimate = 0.09, 95% [CI −0.04, 0.21], $z = 1.36$, $P = 0.173$).

The mean utility score derived from the EQ-5D at pre-treatment was 0.51 (SD = 0.31) for the EXP-CBT group and 0.47 (SD = 0.29) for the T-CBT group. Corresponding figures at 15MFU were 0.57 (SD = 0.29) for the EXP-CBT group and 0.48 (SD = 0. 33) for T-CBT group. The between-group difference on EQ-5D utility score was non-significant (estimate = 0.05, 95% CI [−0.04; 0.15], $z = 1.08$, $P = 0.281$).

Total accumulated costs over the study period

The accumulated total costs in the two groups and cost differences between EXP-CBT and T-CBT are presented in Table 2. Bootstrapped regression models indicated that there was no significant difference in total cost change in EXP-CBT compared to T-CBT over the 15 months study period (−1477; 95% CI [−7444, 4490], $z = -0.49$, $P = 0.628$). Looking more closely at specific types of costs (see Table 2), significantly lower costs were observed in EXP-CBT compared to T-CBT for work cutback (−1388; 95% CI [−2743, −34], $z = -2.01$, $P = 0.045$) and domestic loss (−547, 95% CI [−1058, −37], $z = 2.10$, $P = 0.036$), whereas therapist costs were significantly lower in T-CBT than in EXP-CBT (150, 95% CI [3297], $z = 2.00$, $P = 0.046$). Analyses of dose-response relationships showed significant associations between responder status and total accumulated costs: responders (FIQ decrease ≥14%; $n = 71$ in EXP-CBT, $n = 60$ in T-CBT) had lower total costs (OR

Table 2
Accumulated total costs by type of expenditure over the trial period, USD ($), and cost differences between EXP-CBT and T-CBT over the 15-month trial period, analyzed with bootstrapped mixed models. Data collected on a 1-month basis and estimated to total accumulated costs using linear interpolation.

	EXP-CBT (n = 118)		T-CBT (n = 115)					
	Mean (SD)	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**	**Estimate**	**Z**	***p*-value**	**95% CI**
Direct medical	6132 (6108)	4582 (1957 - 7714)	7441 (8092)	4712 (1939 - 10532)	−1309	−1.43	0.153	−3106 488
Health care visits	5663 (5909)	4242 (1936 - 7357)	6916 (7843)	4418 (1561 - 9665)	−1253	−1.41	0.159	−2997 492
Medications	469 (799)	252 (148 - 492)	525 (860)	303 (86 - 632)	−56	−0.52	0.606	−268 156
Direct non-medical	506 (1326)	0 (0 - 309)	1091(3141)	0 (0 - 667)	−585	−1.87	0.062	−1200 30
Indirect non-medical	20 902 (21 262)	12 311 (3535 – 33 211)	20 632 (19 382)	14 242 (5131 - 32 519)	270	0.10	0.917	−4829 5369
Unemployment	8610 (16 243)	0 (0 - 6312)	7813 (16 318)	0 (0 - 0)	797	0.38	0.708	−3368 4962
Sickleave	7829 (16 087)	114 (0 - 7176)	6420 (12 742)	596 (0 - 8255)	1409	0.75	0.454	−2281 5098
Work loss	2506 (4113)	767 (0 - 3502)	3894 (6345)	1130 (0 - 4901)	−1388	−2.01	**0.045**	−2743 −34
Domestic loss	1957 (1944)	1182 (561 - 2640)	2505 (1960)	1901 (979 - 3768)	−547	−2.10	**0.036**	−1058 −37
Total	27 540 (23 296)	21 378 (7537- 41 200)	29164 (24 206)	22 490 (10 915 – 40 615)	−1624	−0.53	0.594	−7587 4339
Therapist cost	844 (749)	660 (241 – 1178)	697 (449)	634 (411 – 857)	150	2.00	**0.046**	3 297
Total costs incl. therapist costs	28 385 (23 346)	21 665 (8840 – 42 034)	29 861 (24 145)	22 550 (11 231- 41 061)	−1477	−0.49	0.628	−7444 4490

EXP-CBT, internet-delivered exposure-based cognitive behavior therapy. T-CBT, internet-delivered traditional cognitive behavior therapy

0.9999845, $z = -2.30$, $P = 0.022$). However, this association was not observed for participants who deteriorated (FIQ increase ≥14%; $n = 10$ in each condition) (OR 1.000007, z = 0.80, $P = 0.424$). More details regarding differences in total accumulated costs between EXP-CBT and T-CBT are presented in Table 2. Costs at pre-treatment, post-treatment and 15MFU for EXP-CBT and T-CBT are detailed in Table 3.

Cost-effectiveness

ICER of one additional responder

From a societal perspective, the bootstrapped regression analyses estimated the ICER as −1477/0.09 = –$16,884. This means that for each additional treatment responder, as defined by a 14% reduction in the FIQ, the societal cost was $16,884 lower in EXP-CBT than in T-CBT. When viewed from a health care provider perspective, the corresponding ICER was −1162/0.09 = –$12,911. Fig. 1 illustrates the scatterplot of simulated ICERs across all four quadrants, indicating the uncertainty surrounding the estimated parameters.

As seen in Fig. 1, a majority of the simulated ICERs appeared in the southeast quadrant (62% when analyzed from a societal perspective, 83% when analyzed from a health care provider perspective), reflecting a context where EXP-CBT is associated with higher effectiveness and lower costs compared to the control condition, indicating that EXP-CBT has a high probability of being cost-effective treatment compared to T-CBT. Only 3% (societal perspective) and 1% (health care provider perspective) of the ICERs appeared into the northeast quadrant, reflecting a situation where EXP-CBT is associated with less effectiveness and higher costs compared to T-CBT.

The same models were utilized to create the acceptability curves. As depicted in Fig. 2, EXP-CBT had a 69% probability of being cost-effective

Table 3
Detailed cost expenditures at pre-treatment, post-treatment and 15-month follow-up for online exposure therapy and online traditional CBT, respectively.

	Pre-treatment				**Post-treatment**				**15-month follow-up**			
	EXP-CBT (n = 137)		T-CBT (n = 137)		EXP-CBT (n = 132)		T-CBT (n = 129)		EXP-CBT (n = 119)		T-CBT (n = 116)	
	Mean (SD)	***Median (IQR)***	***Mean (SD)***	***Median (SD)***	***Mean (SD)***	***Median (IQR)***	***Mean (SD)***	***Median (IQR)***	***Mean (SD)***	***Median (IQR)***	***Mean (SD)***	***Median (IQR)***
Direct medical	364 (564)	171 (18, 505)	462 (513)	294 (59, 669)	383 (550)	168 (20, 597)	462 (626)	230 (28, 641)	450 (501)	262 (22, 691)	540 (705)	271 (14, 770)
Health care visits	327 (558)	146 (0, 449)	413 (468)	225 (0, 619)	346 (538)	146 (0, 561)	426 (608)	225 (0, 570)	428 (498)	237 (0, 685)	510 (698)	225 (0, 714)
Medications	37 (80)	19 (8, 40)	50 (124)	24 (8,56)	38 (80)	17 (8, 39)	37 (51)	20 (6, 45)	20 (31)	10 (2, 24)	30 (79)	12 (3, 35)
Direct non-medical	51 (160)	0 (0, 0)	47 (149)	0 (0, 0)	34 (99)	0 (0, 0)	85 (285)	0 (0, 0)	27 (91)	0 (0, 0)	68 (332)	0 (0, 0)
Indirect non-medical	1488 (1547)	915 (333, 2335)	1434 (1551)	855 (268, 2163)	1375 (1731)	521 (58, 2394)	1319 (1457)	590 (238, 2430)	1476 (1727)	521 (65, 3128)	1360 (1669)	506 (133, 2791)
Unemployment	555 (1290)	0 (0, 0)	502 (1232)	0 (0,0)	509 (1121)	0 (0, 0)	498 (1174)	0 (0, 0)	667 (1420)	0 (0, 0)	541 (1238)	0 (0, 0)
Sickleave	515 (1125)	0 (0, 598)	398 (974)	0 (0, 400)	573 (1345)	0 (0, 413)	337 (806)	0 (0, 209)	516 (1207)	0 (0, 164)	487 (1198)	0 (0, 415)
Work loss	202 (358)	0 (0, 280)	293 (563)	0 (0, 335)	151 (334)	0 (0, 160)	304 (630)	30 (0, 262)	188 (432)	0 (0, 200)	200 (452)	0 (0, 190)
Domestic loss	215 (238)	44 (121, 302)	240 (259)	164 (51, 310)	141 (201)	62 (15, 187)	180 (230)	34 (112, 275)	105 (136)	51 (0, 171)	132 (122)	85 (34, 209)
Total	1902 (1691)	1269 (662, 3234)	1943 (1827)	1310 (627, 3165)	1792 (1864)	1112 (335, 3185)	1867 (1754)	1173 (489, 3164)	1951 (1889)	1314 (368, 3460)	1968 (2088)	1051 (403, 3536)
Therapist cost (n = 137)					806 (746)	591 (235, 1070)	656 (454)	568 (379, 837)				

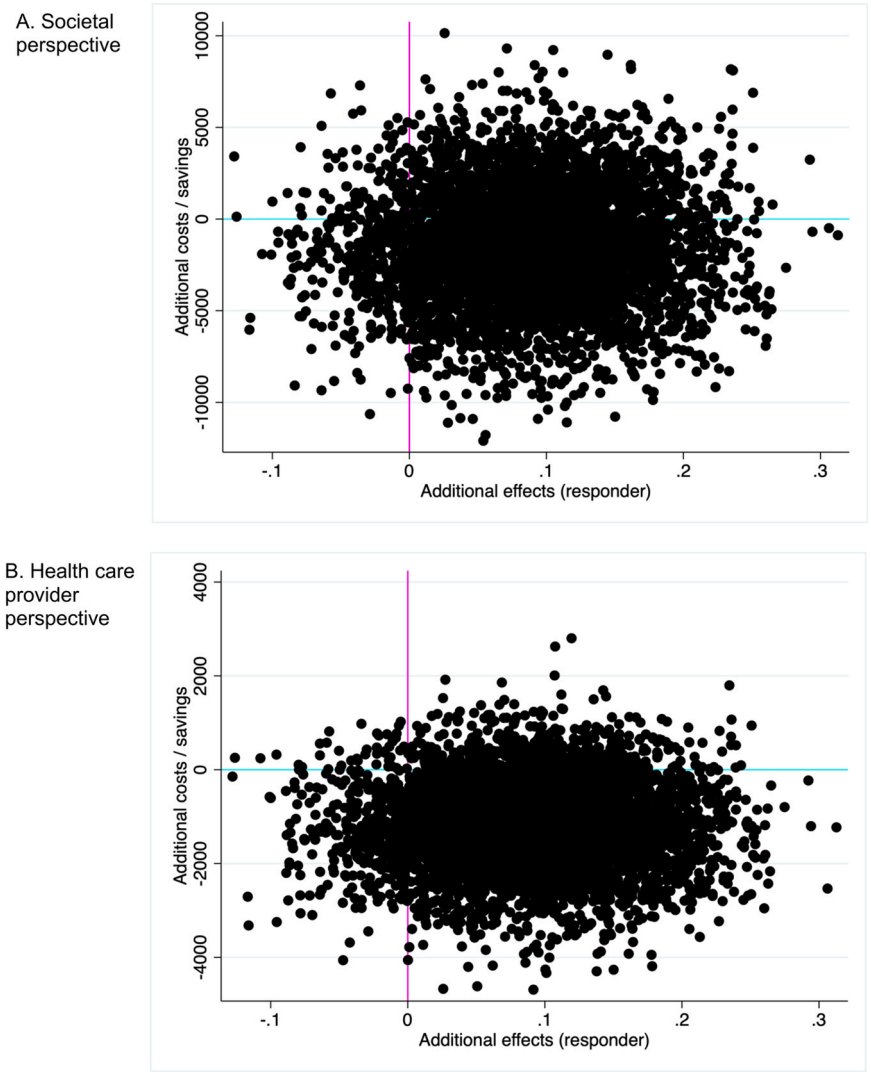

Fig. 1. Cost-effectiveness planes of 5000 bootstrap replicated incremental cost-effectiveness ratios comparing online exposure therapy with online traditional CBT, where effects refer to responder status on the FIQ, from (A) the societal and (B) the health-care provider perspective. Each plane has four quadrants. Dots in the northwest (NW) quadrant indicate that the main treatment (EXP-CBT), while more effective on average, also leads to higher average costs compared to the alternative (T-CBT). Dots in the northeast (NE) quadrant indicate that the main treatment is more costly but also more effective on average, as compared to the alternative. Dots in the southwest (SW) quadrant represent situations where the main treatment is less expensive and also less effective on average. Dots in the southeast (SE) quadrant are instances where the main treatment demonstrates both a lower average cost and higher average efficacy, which is the most favorable outcome for the main treatment as compared to the alternative.

from a societal perspective with a willingness-to-pay (WTP) value of zero ($0). When the perspective was adjusted to a health care provider standpoint, the probability of EXP-CBT being cost-effective increased to 90% with a WTP of zero.

ICER of one additional QALY

The above analyses were repeated using EQ-5D as outcome. From a societal perspective, the cost-utility analysis resulted in an estimate of −1477/0.05 = –$28,763, indicating that for each additional QALY gained through EXP-CBT, the societal cost was $28,763 lower in EXP-CBT than in T-CBT. When the analysis was limited to a health care provider perspective, the corresponding estimate was −1162/0.05 = –$23,240. The distribution of the estimated ICERs is shown in the ICER plane in Fig. 3, where 61% of the cost-utility ICERs are located in the southeast quadrant when analyzed from the societal perspective, and 81% when analyzed from a health care provider perspective. Again, only a small fraction of the ICERs (3% in the societal perspective and 1% in the health care provider perspective analysis) fell into the northwest quadrant.

Also with QALYs as outcome, EXP-CBT had a 69% probability of being cost-effective from a societal perspective, even with a WTP of $0 (see Fig. 4). From the health care provider perspective, EXP-CBT had an 90% probability of being cost-effective with a WTP of $0.

Discussion

The current study represents the first attempt to evaluate the cost-effectiveness of online exposure therapy vs. online traditional CBT for fibromyalgia. Results indicate the treatments are fairly similar regarding total costs and effectiveness, but that online exposure therapy may be cost-effective to online traditional CBT, as each incremental treatment responder was associated with a societal cost reduction of $16,884. There was no significant difference in total accumulated costs, but exposure therapy had significantly lower costs for work cutback and domestic loss, whereas T-CBT had lower therapist costs. The main strengths of this study were the comparison of two active treatments in a randomized design, a large sample size and the use of both a full societal perspective (including all direct and indirect costs) as well as a health

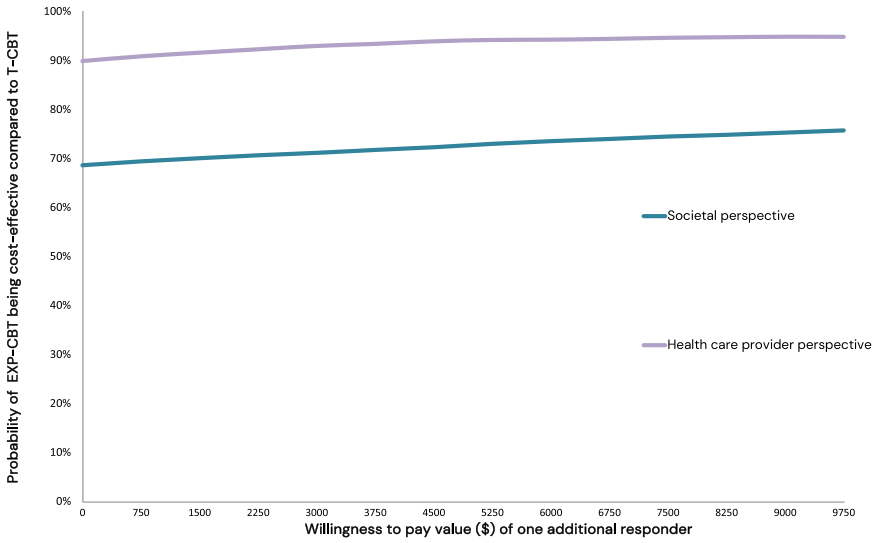

Fig. 2. Cost-effectiveness acceptability curve comparing online exposure therapy with online traditional cognitive behavior therapy. Additional responder refers to 1 additional case of 14% decrease on the FIQ from pre-treatment to 15MFU. NOTE: Societal perspective means that all direct and indirect costs are included in the calculation. Health care provider perspective includes only the direct medical costs, including the cost of the intervention. Abbreviations: EXP-CBT, online exposure therapy, T-CBT, online traditional cognitive behavior therapy.

care provider perspective. Moreover, the use of a disorder-specific instrument for measuring outcome (FIQ) in addition to a general health measurement enabled information on what can be gained for this particular disorder.[44]

When interpreting the ICER estimate, it is important to bear in mind that in cases where the difference in effect is small (as in the current study, with a difference in mean proportion of responders between conditions of 0.09), the denominator will by nature lead to a large ICER (as a denominator close to zero will yield a large quotient). And in cases where even a small cost difference favors the experimental condition, such as in the current study where EXP-CBT had lower total accumulated costs than T-CBT, the negative numerator (in the current study –$1477) divided by a denominator close to zero will equal a large negative quotient suggesting that each treatment responder is associated with substantially lower costs than the alternative treatment. This should however not be interpreted as large societal cost gains are made for each treated patient in EXP-CBT compared to T-CBT, but it rather reflects that gaining a treatment responder is a seldom occurring event when providing Exp-CBT instead of T-CBT. To nuance the picture, the ICER should be interpreted in the light of EXP-CBT having about 70% probability of being cost-effective from a societal perspective across a range of willingness to pay scenarios. In other words, even if society were willing to pay large amounts for EXP-CBT, then T-CBT would still have about a 30% probability of being more cost-effective.

Besides being a cost-effective alternative to face-to-face-treatment,[45] online interventions have other important health economic benefits. Treatment is independent of geographical distance, which reduces salary loss due to time taken from work as well as travel expenses. Moreover, there is no risk of insufficient use of therapist time due to canceled appointments, which further enhances efficient use of limited health care resources. Several simulation and randomized controlled cost-effectiveness studies for other conditions than FM have suggested that online treatment is cost-effective compared to face-to-face treatment.[46–50] Although not addressed in the current study, against this backdrop it is reasonable to believe that both EXP-CBT and T-CBT might be competitive treatment options compared to face-to-face CBT from a cost-effectiveness perspective. Given the relatively small difference in costs and effects between EXP-CBT and T-CBT in the current study, one might consider basing decisions between treatments also on other factors such as patient preferences and the ease of training therapists.

To our knowledge, exposure therapy has not been previously compared to traditional CBT for FM regarding cost-effectiveness, regardless of delivery format. Our study however aligns with our previous health economic study[19] in that the lion's share of the costs were indirect costs (productivity loss), and that there were slight observed reductions in indirect costs over time while participants made substantial within-group improvements. Regarding other previous health-economic evaluations on CBT for FM, effects on QALYs have been mixed but with the majority of studies indicating different variants of CBT to be associated with significantly less costs over time than pharmacological treatment and usual care.[51–54] Calculations of indirect cost expenditures have differed between studies, which precludes straightforward comparisons to the results of the current study. A recent systematic review and meta-analysis on economic evaluations of non-pharmacological interventions for FM[55] found only two studies comparing psychological interventions, emphasizing the need for more high-quality cost-effectiveness studies on psychological treatments for FM. Among studies comparing a psychological intervention to another or to usual care, mean health care costs for psychological interventions ranged from $961 to $3542, situating the current study's results at the higher end.

Widening the perspective to chronic pain, Dear et al.[56] performed a cost-effectiveness analysis of an internet-delivered pain management program, comparing clinician support levels to a waitlist control. Achieving a $\geq$ 30% reduction in disability, depression, anxiety, and pain was associated with cost savings for self-guided (ICER: -$404 to -$808 AUD) and optional-guided formats (ICER: -$314 to -$541 AUD), with a small fixed cost for clinician-guided format (ICER: $88−$225 AUD). Paganini et al. evaluated the cost-effectiveness and cost-utility of guided and unguided online acceptance and commitment therapy versus a waitlist control from a societal perspective. The guided intervention had an ICER of €45 and an incremental cost-utility ratio (ICUR) of €604, while the unguided version had an ICER of €−2933 and an ICUR of −27, 076. Both studies provide valuable insights into the cost-effectiveness of varying clinician support levels. Hess Engström et al.[57] conducted a cost-effectiveness analysis of guided CBT for vulvodynia, added to regular care, versus regular care alone. The ICER for a clinically meaningful change in pain acceptance was estimated at €260.77, with fewer post-intervention midwife visits.

Analyses of dose-response relationships showed significant associations between reliable change of FM symptoms and cost changes in both

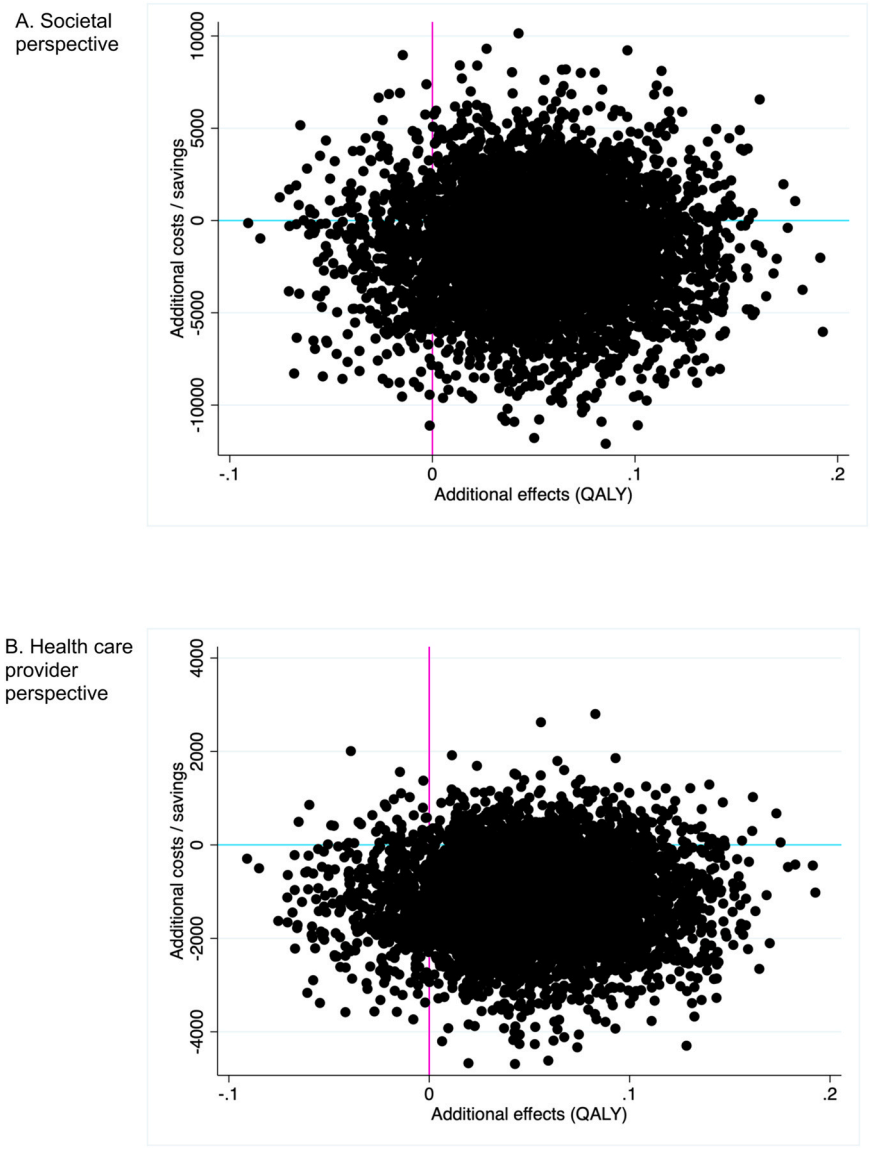

Fig. 3. Cost-effectiveness planes of 5000 bootstrap replicated incremental cost-effectiveness ratios comparing online exposure therapy with online traditional CBT, where effects represent quality-adjusted life years (QALYs) as assessed by the EQ-5D, from (A) a societal and (B) a health care provider perspective, respectively.

groups. More specifically, participants who were treatment responders had lower total accumulated costs at 15MFU. Thus, results suggest that a strive for symptom reduction in CBT for FM may be beneficial from a cost perspective, and that efforts to develop more effective interventions might not just lead to symptom reduction in patients with FM but also to lower societal costs. Neither treatment seemed to be associated with total cost savings over the whole time horizon, whereas direct medical costs appear to increase slightly over time in both groups. Although change over time within group was not evaluated in the present study, the findings highlight the importance of having long-term follow-up periods when conducting health-economic evaluations of psychological treatments.

Some limitations should be considered when interpreting the results from the present study. First, there was a slight trend towards higher baseline scores on the FIQ in the T-CBT group, although no corresponding trend was observed towards higher costs at baseline in the T-CBT group. The current analysis did not control for baseline differences, thus; there is a possibility that these observed random differences may have impacted the results in favor of EXP-CBT. Second, the use of linear interpolation and area under the curve (AUC) method to estimate accumulated total costs required data from all three time points, and, considering the data loss of 14% at 15MFU one could argue that there should be an imputation of missing data to reduce bias in the results. However, as the data loss was limited and equally distributed between the two groups the use of complete case analysis was regarded as acceptable. Third, the sample size of the current study was based on the efficacy analysis for the primary outcome study[23] and not on the cost-effectiveness analysis, as is often the case for economic evaluations performed alongside economic trials. A fourth potential limitation was the use of self-recruitment, and, as in our previous study, our sample showed lower rates of sick leave and unemployment than in other CBT trials for FM,[58–61] suggesting that the direct and indirect costs may not fully reflect those of patients with FM in pain clinics or primary care. Also, the proportion of participants with a college or university degree was relatively high compared to most FM psychological treatment studies.[52,54,61,62] Still, the sample was clinically comparable to previous trials with consecutive clinic patients in terms of FM symptoms[11], and the inclusion of patients with somatic and/or psychiatric comorbidities commonly linked to FM[63,64] likely improved the external validity. A venue for future research is to test the treatments in a clinical context and compare the cost-effectiveness to treatment as usual. Relatedly, cost-effectiveness analyses for more severe patients in specialized pain

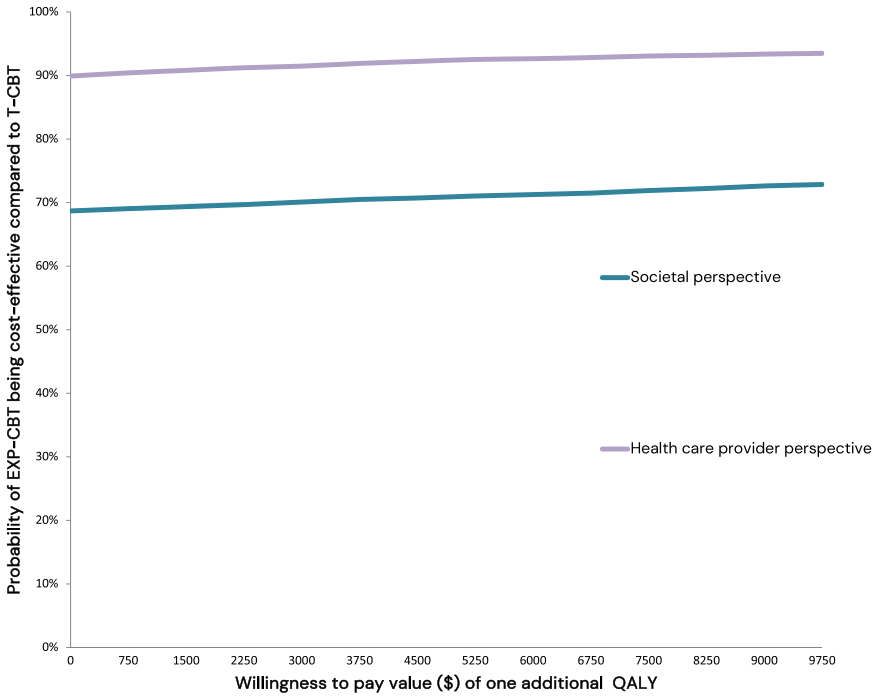

Fig. 4. Cost-effectiveness acceptability curve comparing online exposure therapy (EXP-CBT) to online traditional CBT (T-CBT), where responder refers to one additional quality-adjusted life year (QALY). Note: Societal perspective means that all direct and indirect costs are included in the calculation. Health care provider perspective includes only the direct medical costs, including the cost of the intervention. Abbreviations: EXP-CBT, online exposure therapy, T-CBT, online traditional cognitive behavior therapy.

clinics should be undertaken before generalizing the findings from the current study to the whole FM population. The use of self-report questionnaires rather than public registers in cost-effectiveness studies is debated, as memory bias could potentially reduce the accuracy of cost data. Nonetheless, given the study's randomized design this risk should be evenly distributed across both groups. Although this method is also considered to be valid[65,66] and recommended,[67] future studies could benefit from triangulating data from several sources.

In conclusion, online exposure therapy for FM may be a cost-effective alternative compared to online traditional CBT. However, given the similarity in effects and costs between the two groups, neither EXP-CBT nor T-CBT could be said to be unambiguously cost-effective in comparison to the other.

Disclosures

This study was funded by Riksbankens Jubileumsfond (RJ; MHL; identifier: P20–0297) which required findings from the trial to be published open access. In all other regards, the funder had no role in the study conception, design, data collection, analysis, or publication process.

E.H-L., B.L., and E.A. have co-authored a self-help book for pathological health anxiety that is based on exposure-based cognitive behavior therapy and for which they receive royalties. E.H-L. and B.Lj. are shareholders of Hedman-Lagerlöf och Ljótsson Psykologi AB which licences exposure-based cognitive behavior therapy for irritable bowel syndrome.

CRediT authorship contributions statement

Conception and design: M. H-L., E. H-L., M.B., and E.A. Acquisition of data: M.H-L., E.H-L., M.B., and E.A. Statistical analysis: M. H-L. Drafting of the manuscript: M.H-L. Interpretation, critical revision for intellectual content, and approved the final manuscript: M.H-L., E.H-L. M.B. and E. A.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT and Paperpal in order to improve readability and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of Competing Interest

None.

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Open materials and methods

The components of the research methodology needed to reproduce the reported procedures and analyses are not publicly available, but can be available from the corresponding author upon request.

Data Availability

The data used in this study are not publicly available. Reasonable requests may be directed to the corresponding author, and will be considered on a case-by-case basis, in accordance with the local policies of the sponsor and the relevant Swedish and European Union data protection and privacy legislation.

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