

STUDY PROTOCOL

RANDOMIZED CONTROLLED TRIAL OF INTERNET-DELIVERED EXPOSURE-BASED COGNITIVE BEHAVIOR THERAPY VS. INTERNET- DELIVERED TRADITIONAL COGNITIVE BEHAVIOR THERAPY FOR PATIENTS WITH FIBROMYALGIA

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Study protocol

Randomized controlled trial of internet-delivered exposure-based cognitive behavior therapy vs. internet-delivered traditional cognitive behavior therapy for patients with fibromyalgia

Summary

Fibromyalgia (FM) is a common medical condition characterized by chronic generalized musculoskeletal pain, fatigue, and a series of additional somatic and psychiatric problems that give rise to distress, functional impairment, and substantial societal costs. The most extensively evaluated treatment for FM is traditional cognitive behavior therapy (T-CBT) which typically appears to have small to moderate effects when compared to waitlist, attention control, treatment as usual or other active nonpharmacological therapies. Internet-delivered exposure-based cognitive behavior therapy (Exp-CBT) where the patient willingly and systematically engages with stimuli associated with pain and pain-related distress has shown promising controlled effects versus a waiting-list but has never been compared to T-CBT in a randomized controlled trial. In this randomized controlled trial, self-recruited adults with FM (N=260) are randomly assigned (1:1) to 10 weeks of internet-delivered Exp-CBT or internet-delivered T-CBT and complete self-report questionnaires to measure symptoms and therapeutic processes up to 12 months after treatment. Primary outcome is the relative effect of Exp-CBT and T-CBT on FM severity as modelled using linear mixed models fitted on weekly Fibromyalgia Impact Questionnaire sum scores over the treatment period, testing the hypothesis of Exp-CBT superiority based on the coefficient for the time \times group interaction. Cost-effectiveness and mediational processes are investigated in secondary analyses. We expect this trial to be of notable clinical significance as it will provide valuable information about the value of Exp-CBT in helping patients with FM as compared to using other interventions.

Overview of the field

Fibromyalgia: a common, disabling, and costly chronic pain condition

Fibromyalgia (FM) is a chronic pain syndrome affecting approximately 2-4% of the general population, and most typically (90%) women (Queiroz, 2013). The condition is characterized by chronic musculoskeletal pain, stiffness, fatigability, and decreased pain threshold (Smith, Harris, & Clauw, 2011). Diagnostic criteria for FM according to the American College of Rheumatology are the following: 1) generalized pain defined as pain in at least four out of five regions (left and right upper region, left and right lower region; axial region), 2) the symptoms have persisted for at least 3 months, and 3) either at least 7 points on the Widespread Pain Index (WPI) and at least 5 points on the Symptom Severity Scale (SSS) *or* at least 4 points on the WPI and at least 9 points on the SSS (Wolfe et al., 2011). Individuals with FM also commonly experience other somatic and psychiatric symptoms such as disturbed sleep, tension headache, migraine, fatigue, gastrointestinal problems, cognitive impairment, dizziness, low mood, anxiety, and increased sensitivity to stress (Wolfe, Ross, Anderson, Russell, & Hebert, 1995). The condition is associated with functional impairment, substantially lowered quality of life (Hauser et al., 2015), and also notable societal costs due to its effects on health care expenditure, sick leave, and work status (Rivera, Rejas, Esteve-Vives, Vallejo, & ICAF, 2009).

The avoidance of pain is predictive of poor health outcomes

The experience of pain relies on a complex interaction of biological, psychological, and social factors (Gatchel, Peng, Peters, Fuchs, & Turk, 2007). A number of psychological factors have been found to be especially important, including attentional, emotional, and cognitive processes. An important factor in the maintenance of pain over time is pain-related avoidance, i.e., that the patient starts avoiding situations and activities where pain might occur, whereby the avoided

situations and activities by classical and operant conditioning become associated with pain and pain-related distress. Pain-related avoidance often implies a reduction in meaningful activities such as social interaction and work, and often leads to a vicious cycle where a shrinking behavioral repertoire feeds the impact of pain on everyday life, which leads to more avoidance, more attention devoted to pain instead of meaningful activities, and so on (Wicksell et al, 2008). Numerous studies have indicated that pain-related avoidance is predictive of increased pain, increase attention to pain, and increased functional impairment (Geisser, Haig, & Theisen, 2000; Goubert, Crombez, Eccleston, & Devulder, 2004; McCracken, Eccleston, & Bell, 2005; Philips & Jahanshahi, 1985; Prkachin, Schultz, & Hughes, 2007).

Importance of psychological treatment

While pharmacological treatment for FM with antidepressants and anticonvulsants (Arnold, 2006; Goldenberg, Burck, Hardt, Crofford, 2004) can reduce pain and other FM-related symptoms, of those who receive pharmacological treatment for FM, only about 40% experience clinically significant improvement (Arnold, 2006) and the utility of pharmacological treatment has been therefore questioned (Nüesch, Hauser, Bernardy, Barth, & Jüni, 2013). Non-pharmacological treatments are commonly at least as efficacious (Rossy et al., 1999).

Traditional cognitive behavior therapy

Traditional cognitive behavior therapy (T-CBT) is the most widely evaluated psychological treatment for FM with over 40 randomized controlled trials. In the majority of these trials, T-CBT protocols have been composite interventions, based on a combination of treatment components such as relaxation, problem solving, psychoeducation, stress management practices, and cognitive restructuring techniques. A widely used treatment component with relatively robust support has been *pacing*: the systematic dosing of activity level to achieve energy conservation. The patient is encouraged to use particular strategies before, during, and after activities in order to moderate pain (Hammond, 2004).

Bernardy and colleagues published a 2013 systematic Cochrane review and meta-analysis of randomized controlled trials of cognitive-behavioral interventions (including acceptance and commitment therapy) for FM (Bernardy, Klose, Busch, Choy, & Hauser, 2013). Their conclusion was that such treatments give a small but significant added effect on pain, mood, and functional impairment as compared to waitlist control, attention control, treatment as usual or other nonpharmacological therapies. An update was published in 2017 including trials conducted between 2013-2017 (Bernardy, Klose, Welsch, & Hauser, 2017). In this review, CBT was found to provide a clinical benefit over control interventions in reducing some core symptoms and disability at the end of treatment, but did not change the major findings from the original review.

Exposure-based cognitive behavior therapy

Exposure is among the most widely employed treatment components in psychological treatments for common anxiety disorders (Koran et al., 2007; National Collaborating Centre for Mental Health, 2005, 2006, 2011, 2013; Ursano et al., 2004) and has also been evaluated with promising results for several somatic conditions (Bonnert et al., 2016; Craske et al., 2011; Ljótsson, Hedman, et al., 2011). Exposure therapy is based on repeated and maintained confrontation with stimuli that give rise to unwanted responses, and is conducted with the aim of achieving therapeutic effects, usually conceptualized as some sort of new learning. Exposure for somatic conditions implies that the patient systematically engages in exposure exercises, such as by provoking discomfort or feared symptoms, approaching avoided activities and situations in a new manner without resorting to distraction. Exposure also implies refraining

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from so called safety- and avoidance behaviors intended to reduce unwanted emotions or discomfort in the short term. The mechanism of action by which exposure works is not fully understood, but it is commonly hypothesized that repeated exposure leads to an increased tolerance of unwanted emotions or discomfort, and that the patient gradually develops a stronger belief in his or her ability to manage symptoms and situations previously feared or avoided (Tryon, 2005).

Considering that avoidance behavior contributes to maintain pain over time, exposure has been suggested as a key intervention for patients suffering from chronic pain, and has also been evaluated for chronic pain conditions in a few randomized controlled trials (den Hollander et al., 2016; Leeuw et al., 2008; Linton et al., 2008; Woods & Asmundson, 2008). Our research group has previously developed and evaluated exposure-based treatment for patients with FM in a pilot study and subsequent large-scale RCT (Hedman-Lagerlöf et al., 2018; Brjánn Ljótsson et al., 2014), both with promising results as detailed below. Considering that pain-related avoidance behavior exists in many forms including covert processes such as distraction, resisting, and checking, exposure treatment can be tailored to a wide spectrum of individuals with fibromyalgia including those who do not exhibit avoidance that is visible to the eye

Delivering psychological treatment via the internet

Treating patients with psychological methods via the internet has become increasingly common in recent years (Andersson, 2009). Use of the internet to deliver interventions has several advantages, including high cost-effectiveness since the intervention commonly demands less time from the therapist and can be more easily distributed compared to face-to-face treatment. A systematic review by Carlbring and colleagues (2018), demonstrates that therapist-guided treatment often results in effects similar to those of conventional face-to-face treatment. Internet-delivered T-CBT for FM has been evaluated in two RCTs with mixed results (Friesen et al., 2017; Vallejo, Ortega, Rivera, Comeche, & Vallejo-Slocker, 2015).

Our research group has evaluated exposure-based cognitive behavior therapy (Exp-CBT) for FM in two clinical trials. First, in 2012, we completed a pilot trial (regional ethics review board of Stockholm identifier 2011/1499-31/4) where 41 participants with FM took part in a 10-week internet-delivered psychological treatment program that emphasized systematic exposure. Results were indicative of substantial change from pre- to post-treatment ($p < 0.001$) in all outcome domains, with moderate to large standardized effects ($d = 0.65-1.21$) (Brjánn Ljótsson et al., 2014). In the subsequent RCT, 140 participants were randomized to 10 weeks of Exp-CBT or a waiting-list, resulting in large waitlist-controlled effects on FM-symptoms, pain, fatigue, functional impairment and pain-related anxiety. The study also indicated that Exp-CBT, compared to no treatment, is highly cost-effective, and that a reduction in FM-related avoidance was associated with a larger treatment effect. A clear limitation in the current body of knowledge, however, is that exposure-based treatment for FM has not been compared to an active control group. Our knowledge of treatment moderators and mechanisms is also limited.

Summary of background

In conclusion, FM is a common problem with substantial negative consequences. The most widely evaluated psychological treatment for FM is T-CBT which usually has small to moderate controlled effects on pain, mood and functional impairment. Based on one pilot study and one waitlist-controlled RCT, Exp-CBT appears to have promising effects on FM but this treatment has not yet been compared to an active control condition. The present study aims to compare internet-delivered Exp-CBT to internet-delivered T-CBT in a randomized controlled trial. In addition to clinical efficacy, we will also investigate cost-effectiveness and mediational

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processes. Primary hypothesis is that Exp-CBT will be more efficacious than T-CBT in reducing FM severity, i.e., a composite score indicative of symptoms and functional status, as assessed using the primary outcome Fibromyalgia Impact Questionnaire (FIQ).

Overarching aim of the study

The overarching aim of the study is to evaluate the clinical efficacy of internet-delivered exposure-based cognitive behavior therapy (Exp-CBT) compared to internet-delivered traditional cognitive behavior therapy (T-CBT) for patients with fibromyalgia (FM) in a large-scale randomized controlled trial.

Primary research question

Does Exp-CBT, compared to T-CBT, produce a larger reduction in FM severity over the 10-week treatment period? Hypothesis: Yes.

Secondary research questions

- 1) Does Exp-CBT, as compared to T-CBT, produce larger controlled effects on A) pain, B) fatigue, C) quality of life, D) functional impairment, E) depression, and F) anxiety? Exploratory.
- 2) Is Exp-CBT more cost-effective than T-CBT? Hypothesis: Yes.
- 3) What factors moderate the treatment outcome? Hypotheses will be fully formulated and registered prior to the analysis, when the precise modeling approach has been chosen.
- 4) What factors mediate the treatment outcome? Hypotheses will be fully formulated and registered prior to the analysis, when the precise modeling approach has been chosen.

Methods

Design

This is a randomized controlled trial with repeated measurements and two conditions: the experimental group (Exp-CBT) and an active control group (T-CBT). Based on previous trials, we expect an Exp-CBT within-group effect of approximately 16.9 points (Hedman-Lagerlöf et al., 2018) and a corresponding T-CBT within-group effect of no more than 9 points (Castel, Salvat, Sala, & Rull, 2009; King, Wessel, Bhambhani, Sholter, & Maksymowych, 2002; Redondo et al., 2004) on the Fibromyalgia Impact Questionnaire (Burckhardt, Clark, & Bennett, 1991). Given this scenario, Monte Carlo simulation ($n=1000$) of multi-level linear regression analyses with 11 weekly measurements and an expected data loss of 10% at every measurement point after baseline indicated that 130 participants will be needed per arm (Exp-CBT vs. T-CBT) for 80% power in testing the time \times group coefficient ($\alpha=.05$).

Eligibility criteria

The study will be open for adults of at least 18 years diagnosed with FM living in Sweden, with access to the internet and with a completed pre-treatment assessment. Concurrent psychotropic medication is allowed if the dose has been stable for at least 4 weeks before randomization and the participant agrees to keep it constant during treatment. Exclusion criteria are the following: A) severe depression (≥ 30 on the Montgomery Åsberg Depression Rating Scale—Self Rated [MADRS-S] at screening), B) suicidal ideation (≥ 4 on the suicide item of the MADRS-S at screening), C) psychosis, D) alcohol or substance use disorder as primary diagnosis or likely to severely interfere with treatment, E) ongoing psychological treatment, F) pregnancy (>29 wk gestation), G) another somatic condition that requires immediate treatment and/or is deemed to be the primary condition, and H) insufficient knowledge of the Swedish language or insufficient computer skills to benefit from the text-based online treatment.

Outcome measures

- **Composite FM severity: symptoms and functional status (primary outcome).** The Fibromyalgia Impact Questionnaire, FIQ (Burckhardt, Clark & Bennett, 1991). This is a validated and disease-specific instrument known to be reliable and responsive to change (R. Bennett et al., 1996).
- **Pain.** The Fibromyalgia Impact Questionnaire, FIQ-Pain subscale (Burckhardt, Clark & Bennett, 1991) and Brief Pain Inventory-Short Form, BPI-S (Mendoza, Mayne, Rublee, & Cleeland, 2006)
- **Fatigue.** Fatigue Severity Scale, FSS (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989).
- **Anxiety and depression.** The GAD-2 (Kroenke, Spitzer, Williams, Monahan, & Löwe, 2007) and Patient Health Questionnaire-2, PHQ-2 (Kroenke, Spitzer, & Williams, 2003)
- **Functional impairment and quality of life.** The WHO Disability Assessment Schedule 2.0, WHODAS 2 (Üstün et al., 2010), Brunnsvikens Brief Quality of Life Inventory, BBQ (Frykheden, 2014), and EQ-5D (Rabin & Charro, 2009)
- **Pain-related avoidance behavior.** The Psychological Inflexibility in Pain Scale-avoidance subscale, PIPS (Wicksell, Lekander, Sorjonen, & Olsson, 2010)
- **Pacing and overdoing behavior:** Patterns of Activity Measure – Pain: pacing and overdoing subscales, POAM-P/p/o (Cane, Nielson, McCarthy, & Mazmanian, 2013)
- **Pain-related catastrophizing.** Pain Catastrophizing Scale, PCS (Sullivan, Bishop, & Pivik, 1995)
- **Hypervigilance.** Pain Vigilance and Awareness Questionnaire, PVAQ (Roelofs, Peters, McCracken, & Vlaeyen, 2003)
- **Physical activity.** The Godin-Shephard leisure-time physical activity questionnaire (Godin, 2011)
- **Global measure of perceived change.** Patient Global Impression of Change, PGIC (Hurst & Bolton, 2004)
- **Resource use including health care consumption and sick leave.** Trimbos and Institute of Medical Technology Assessment Cost Questionnaire for Psychiatry, TIC-P (Haakart-van Roijen, 2002)
- **Treatment credibility.** Credibility/Expectancy Questionnaire, CEQ (Deville & Borkovec, 2000)
- **Working alliance.** Working alliance inventory – short version, WAI-S (Hatcher & Gillaspay, 2006)
- **Patient satisfaction.** Client satisfaction questionnaire, CSQ-8 (Kelly et al., 2018)
- **Adverse events.** Free-text reports of adverse events and rating of the aversiveness of these events on a 4-point Likert scale as used in previous trials, AE (Hedman-Lagerlöf et al., 2018; Brjánn Ljótsson et al., 2014)

Procedure

Recruitment

Participants are self-recruited. The study will be advertised in newspapers, and information will be spread via patient organizations and health care clinics and clinicians in Stockholm Region. Considering that the study does not involve a medical assessment, applicants will be required to already have been diagnosed with FM by a physician. Those interested will apply to participate by completing an online form to provide informed consent after having been presented with the obligatory patient information. Here, applicants confirm that they have been

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given an FM diagnosis and subsequently complete a series of self-report screening questionnaires including routine questions concerning sociodemographic characteristics, FM, medical status, and symptoms. Complete applications are reviewed and followed by a structured telephone interview to inform about the study, collect key clinical data, and assess the study eligibility criteria. Applicants who meet all eligibility criteria are informed that they will be included and randomized after they have completed the pre-treatment assessment. The eligibility interview is conducted by a licenced psychologist, resident psychologist, or psychologist- or psychotherapist student under supervision of a licensed psychologist with knowledge of FM and common psychiatric comorbidities. Individuals who are excluded are informed about the reason for this, and referred to routine care services as necessary.

Randomization

Randomization is conducted 1:1 using the www.random.org service, on a cohort-by-cohort basis, by an external person who is blind to participant characteristics.

Table 1. *Measurements*

Questionnaire	Outcome	Reference	SN	PRE	WK	POST	6M FU	12M FU
Efficacy outcomes								
FIQ	Composite FM severity	(Burckhardt et al., 1991)	x	x	x	x	x	x
FIQ subscale	Pain, primary measure		x	x	x	x	x	x
FSS	Fatigue	(Krupp et al., 1989)		x		x	x	x
BPI-S	Pain, secondary measure	(Mendoza et al., 2006)		x		x		
GAD-2*	Anxiety	(Kroenke et al., 2007)		x		x	x	x
PHQ-2*	Depression (outcome)	(Kroenke et al., 2003)		x		x	x	x
WHODAS 2	Functional impairment	(Üstün et al., 2010)		x		x	x	x
BBQ	Quality of life	(Lindner et al., 2016)		x		x	x	x
PGIC	Impression of change	(Hurst & Bolton, 2004)				x		
Screening only								
MADRS-S	Depression (screening)	(Svanborg & Asberg, 1994)	x	a	a	a	a	a
AUDIT	Alcohol use	(Saunders, Aasland, Babor, de la Fuente, & Grant, 1993)	x					
DUDIT	Drug use	(Berman, Bergman, Palmstierna, & Schlyter, 2005)	x					
Primarily used to investigate processes								
PIPS-avoid	Avoidance	(Wicksell et al., 2010)		x	x	x	x	x

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POAM-P-p/o	Pacing and overdoing	(Cane et al., 2013)		x	x	x	x	x
PCS	Catastrophizing	(Sullivan et al., 1995)		x	x	x	x	x
PVAQ	Hypervigilance	(Roelofs et al., 2003)		x	x	x	x	x
C/E	Credibility, expectancy	(Deville & Borkovec, 2000)			w. 2			
WAI-S	Therapeutic alliance	(Hatcher & Gillasp, 2006)			w. 2			
GSLTPAQ	Physical activity	(Godin, 2011)		x	x	x		
Primarily used for health economic analyses								
EQ-5D	HR quality of life (utility)	(Rabin & Charro, 2009)		x		x	x	x
TIC-P	Resource use (societal)	(Haakart-van Roijen, 2002)		x		x	x	x
Other outcomes								
CSQ-8	Patient satisfaction	(Kelly et al., 2018)				x		
AE	Adverse events	(Hedman-Lagerlöf et al., 2018; Brjánn Ljótsson et al., 2014)				x		

6MFU = 6-month follow-up; 12MFU = 12-month follow-up; FM = fibromyalgia; HR = health-related; POST = post-treatment; PRE = pre-treatment; SN = screening / application; WK = weekly assessment (week 1-9). *In this study, we will employ a cut-off of 3 points to identify clinically significant anxiety and depression on the GAD-2 and PHQ-2 respectively. a) Only suicidality item administered; patients contacted if flagged and referred to routine care as needed.

Data management

Personal data will be managed confidentially and each participant is granted a personal code. Personal data and the personal key (“kodnyckel”) will be stored on a secure server, access to which requires double authentication, as employed in previous projects (regional ethics review board of Stockholm identifier 2014/1944-31/5). These data will only be accessed by researchers in the project. All correspondence between participants and therapists will take part via a secure messaging system that employs double authentication, and to which the participant is granted a personal password. Data is stored and managed in accordance to Swedish and European Union data protection and privacy legislation including the Swedish National Board of Health and Welfare guidelines for management of personal data (2 kap. 5 § SOSFS 2008:14). Data derived from self-report questionnaires will be reported in such a way as to not enable the identification of individuals.

Treatment conditions

General structure of internet-delivered treatment

Participants in Exp-CBT and T-CBT are encouraged to work with self-help texts and complete regular homework exercises via a secure treatment platform. Both treatments are 10 weeks long, equally exhaustive, and involve approximately the same level of therapist support. Throughout the treatment, participants communicate with a therapist, who guides the participants through the intervention by means of email-like text messages. Therapists are assigned to only one treatment protocol to prevent contamination. Therapists are licensed

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psychologists, resident psychologists, last-year students of the Swedish master-level psychologist program, or student of the advanced-level Swedish psychotherapist program. All therapists are given thorough education in the treatment protocol and work under the supervision of a licensed psychologist.

Internet-delivered exposure-based cognitive behavior therapy (Exp-CBT)

The Exp-CBT treatment manual is the same as developed and tested previously, as detailed above (Hedman-Lagerlöf et al., 2018). The primary treatment component is exposure to stimuli (situations and activities) that give rise to pain, distress, and unwanted emotional responses. The treatment proceeds in accordance with functional analysis (Haynes & O'Brien, 1990). Exercises are tailored for the patient so that, for example, individuals whose main coping strategy is to be overly active (i.e., persistence behavior) are encouraged to sit down and observe pain and other aversive bodily sensations as they arise. The protocol also includes regular exercises where the participant is encouraged to observe and name physical sensations without acting on them.

Internet-delivered traditional cognitive behavior therapy (T-CBT)

The T-CBT treatment manual has been developed and tested for chronic back pain (Buhrman, Fältenhag, Ström, & Andersson, 2004). This treatment is based on components typical of T-CBT for FM, including relaxation, activity planning or pacing, cognitive restructuring techniques, stress management strategies, and assertiveness training.

Statistical analysis

To evaluate the effect of treatment, data is analyzed using linear mixed-effects regression according to the intention-to-treat principle. For the primary analysis, linear mixed models are fitted on the weekly FIQ sum scores over the treatment period, testing the hypothesis of Exp-CBT superiority based on the coefficient for the time \times group interaction. In a secondary analysis, we will also investigate the proportion of participants in Exp-CBT and T-CBT who achieve a clinically relevant improvement in FM severity, defined as a FIQ sum score reduction of at least 14% (R. M. Bennett, Bushmakina, Cappelleri, Zlateva, & Sadosky, 2009). A health-economic analysis will be concerned with the incremental cost-effectiveness of Exp-CBT as compared with T-CBT using the same definition of clinically relevant improvement as efficacy outcome. Cost-utility will also be assessed as based on quality-adjusted life years derived from utility scoring of the EQ-5D.

Previous experiences

Communication with patients via the internet has become increasingly common in recent years and can be used to successfully treat numerous somatic and psychiatric health problems. Use of the web as treatment platform entails several advantages. It is health economically attractive since treatment can be offered more widely, including to geographically remote areas. Access to effective treatment is hence not limited to urbanized areas or particular clinics.

The pilot study that we completed in 2012 investigated the effects of Exp-CBT for 41 individuals with FM (regional ethics review board of Stockholm identifier 2011/1499-31/4). Results were indicative of moderate to large within-group effects on FM symptoms. The randomized controlled trial completed in 2016 (regional ethics review board of Stockholm identifier 2015/1528-31/1) was indicative of large between-group effect sizes in terms of FM symptoms (including pain), fatigue, functional impairment, pain-related anxiety and

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psychological flexibility in pain.

Primary investigator for this project is Maria Hedman-Lagerlöf, licensed psychologist and PhD at Karolinska Institutet (KI), Stockholm, Sweden. She initiated the pilot study completed in 2012 and led the large-scale RCT that was completed in 2016.

Brjánn Ljótsson, licensed psychologist and associate professor at KI has completed several trials of exposure-based treatment for irritable bowel syndrome (Ljótsson, Andersson, et al., 2011; Ljótsson, Andréewitch, et al., 2010; Ljótsson, Falk, et al., 2010; Ljótsson, Hedman, et al., 2011; B Ljótsson et al., 2014). Taken together, these studies indicate that exposure can be effective as administered either via the internet or in a group format. This treatment has documented effects on gastrointestinal symptoms, symptom-related anxiety, avoidance behaviors, quality of life, and comorbid psychiatric problems. The effects of this treatment have also been found to be maintained over time (Ljótsson, Andersson, et al., 2011) and to be associated with socioeconomic gains (Andersson et al., 2011). Brjánn Ljótsson has also taken part in internet treatment studies for panic disorder (Bergström et al., 2010), obsessive-compulsive disorder (Andersson et al., 2012), social anxiety disorder (Hedman, Andersson, Ljótsson, et al., 2011), and health anxiety (Hedman, Andersson, Andersson, et al., 2011).

Erik Hedman-Lagerlöf, licensed psychologist at Gustavsberg primary care clinic and professor in psychology at the department of clinical neuroscience at KI. Professor Hedman-Lagerlöf's research has primarily focused on Internet-delivered treatment and the implementation of psychological treatment in a primary care. Erik Hedman-Lagerlöf has worked alongside Brjánn Ljótsson in all projects mentioned above.

Erland Axelsson, licensed psychologist and PhD at Liljeholmen primary care clinic, affiliated with KI. His primary research and clinical interests are in behavioral medicine, and the relationship between psychological processes and physical complaints. Dr Axelsson exhibits extensive competence in scientific and statistical methods, has been involved in over 10 randomized controlled trials of psychological interventions including the 2016 RCT of Exp-CBT for FM (Hedman-Lagerlöf et al., 2018), and has – under EHL – led the largest published RCT of Exp-CBT for health anxiety.

Monica Buhrman, PhD, licensed psychologist and associate professor, senior lecturer at Uppsala University has led and completed several randomized controlled trials evaluating psychological interventions for chronic pain (Buhrman et al., 2012; Buhrman et al., 2004; Buhrman, Nilsson-Ihrfeldt, Jannert, Strom, & Andersson, 2011; Buhrman et al., 2013) and developed the T-CBT protocol intended to constitute the control condition in the present trial. Dr. Buhrman is also appointee of the Swedish national expert group for the development of guidelines for the treatment of FM.

Ethical considerations

This project will be conducted in accordance with the declaration of Helsinki, and Swedish and European Union legislation pertaining to the management of personal data. The RCT will also be preregistered at ClinicalTrials.gov.

Participants confirm via an online form that they have been diagnosed with FM by a physician. Informed consent will be a prerequisite for data collection and inclusion in the study. If the applicant meets exclusion criteria, he or she is informed of this and referred to routine care services as needed. At the post-treatment assessment as well as weekly during treatment,

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patients are given the opportunity to provide free-text written reports of adverse events. In the case of acute deterioration, an individual assessment will be conducted by a licensed psychologist or resident psychologist under supervision, and the participant will be referred to routine care services as needed.

Previous data suggest that Exp-CBT is associated with few negative effects (Hedman-Lagerlöf et al., 2018; Brjánn Ljótsson et al., 2014). The control intervention (T-CBT) has been previously found to be efficacious for chronic pain (Buhrman et al., 2004) and is easily matched to Exp-CBT in terms of readability, image content, and length so as to achieve a fair control condition. Risks associated with this project are thus deemed small in relation to the potential gains. In order to ensure safe management of data, communication via the internet is encrypted access to the treatment web platform requires two factor authentication (electronic identification). Personal passwords are confirmed via SMS. All data will be presented in a manner that does not make it possible to identify specific participants.

Our experience from having conducted several studies at the Internet psychiatry unit for somatic conditions such as irritable bowel syndrome as well as psychiatric conditions such as panic disorder and health anxiety is that text-based online communication, which enables more regular interaction than conventional face-to-face treatment, generally functions well to monitor the health and wellbeing of participants, and to ensure that serious adverse events do not arise.

We expect that a positive outcome of this trial would ultimately contribute to a large patient group being able to access effective treatment with excellent scalability. We thus consider the potential harms to be acceptable when considered in relation to the potential gains of delivering an effective form of Exp-CBT to this patient group.

Clinical implications

Individuals with FM suffer much from their disease which leads to impairment and typically lowered mood and quality of life. Even if T-CBT has been found to be efficacious in a number of studies this treatment is not widely available. In previous Swedish research projects, there are several examples of online treatments delivered in a similar format as Exp-CBT that have successfully, and relatively swiftly, been implemented in a routine care setting, such as that of the Internet psychiatry unit where 10,000 patients have completed treatment since 2008. Thus, in our experience, this type of treatment can benefit patients and lead to notable societal gains by increasing access to evidence-based care.

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