Study protocol, version 2

Randomized Controlled Trial of Internet-delivered Exposure-based Treatment vs. Standardized Education for Distress Related to Somatic Symptoms in Primary Care

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Study protocol

Randomized controlled trial of internet-delivered exposure-based treatment vs. standardized education for distress related to somatic symptoms (SOMEX1)

Summary

The annual societal cost of medically unexplained symptoms in Sweden is approximately 40 billion SEK (1), i.e., similar to the annual cost of cancer (2). Prevalent chronic diseases like asthma and diabetes are also commonly associated with somatic symptoms that lead to significant distress and pervasive behavioral changes that result in functional impairment and place added strain on the health care system. Exposure-based treatment, where the patient willingly engages with stimuli that give rise to unwanted physical sensations or distress, has shown promise in reducing somatic symptom load and increasing quality of life in several conditions where patients commonly report substantial distress related to somatic symptoms, such as in asthma (3), musculoskeletal pain (4), and functional gastrointestinal syndromes (5). In routine care, however, access to such exposure-based treatment is limited. One reason for this is probably that there exists no flexible exposure-based treatment protocol that can be easily tailored to suit a wide spectrum of patient groups who suffer from distress related to recurrent somatic symptoms. In a recent single group feasibility trial (N=33) at Karolinska Institutet, Sweden, we found that such a tailored exposure-based treatment delivered in an online text-based format can be acceptable, with high treatment adherence, adequate treatment satisfaction, large and lasting within-group improvement, and no serious adverse events. This is a randomized controlled trial (N=160) where we aim to test if the same tailored internet-delivered exposure-based treatment is more efficacious than a standardized education control for adult patients with clinically significant distress related to somatic symptoms in a primary care setting. Primary outcome is change in self-rated somatic symptom burden as modelled using linear mixed models fitted on weekly Patient Health Questionnaire 15 sum scores over the treatment period. Long-term efficacy is assessed up to one year after treatment and cost-effectiveness is investigated based on the incremental cost-effectiveness ratio. We expect this trial to be of notable clinical importance as it will be indicative of the usefulness of a broad exposure-based treatment protocol for distress related to somatic symptoms in primary care.

Overview of the field (background)

Recurrent distress associated with somatic symptoms: a common and costly problem

Approximately one fifth of primary care patients seek care for symptoms that cannot readily be given a medical explanation (6, 7). In addition, primary care is tasked with offering care for prevalent chronic diseases such as asthma and diabetes where somatic symptoms often lead to distress and pervasive behavioral changes. Though a concern with somatic symptoms can be fully warranted, helpful, and transient, it can also be persistent and lead to much unnecessary suffering. Existing treatments commonly yield insufficient effects on medically unexplained symptoms (8). Based on inflation-adjusted British estimates (1), the annual Swedish societal cost of medically unexplained symptoms is probably about 40 billion SEK, i.e., similar to the annual cost of cancer (2).

Symptom preoccupation as a therapeutic target

Psychological factors – in particular the preoccupation with symptoms – have been found to affect the perception and intensity of a large number of physical symptoms, both with and

without a clear medical genesis (9). In pain, it has for example been found that fear and the preoccupation with symptoms can have a more substantial predictive value for chronicity than pain itself (10). In general, in individuals who suffer from clinically significant symptom preoccupation, behaviors intended to evaluate symptoms, seek information about symptoms, or avoid discomfort have been found to often contribute to worsened function and increased symptom burden in the long term (11).

Diagnosis-specific exposure-based treatment often efficacious
This makes exposure, where the patient willingly and systematically approaches stimuli that give rise to unwanted symptoms or discomfort while refraining from acting on symptoms, a logical intervention. There are several examples where exposure-based treatment has been found to be efficacious when protocols were written to suit a particular group of patients where distress associated with somatic symptoms is common, e.g., a particular functional somatic syndrome in terms of fibromyalgia and irritable bowel syndrome (4, 5), or a chronic somatic condition such as asthma or atrial fibrillation (3, 12). Typically, effects on symptoms and the preoccupation with symptoms have been large (3-5, 12), and there is evidence to suggests that a reduction in somatic symptom burden may have been mediated by a reduction in symptom preoccupation or behaviors that serve to reduce distress in the short term (13).

Need for a more flexible exposure-based approach
Generalist primary care clinics typically do not have the resources necessary for administering specific psychological treatments for a large number specific functional somatic syndromes or chronic somatic conditions (14). We suspect that a more general treatment protocol that can be tailored to suit a wide spectrum of physical symptoms could dramatically improve access to exposure-based treatment for patients with distress related to somatic symptoms. This may be particularly true if treatment can be delivered via the internet, which requires less therapist time but often results in similar effects as face-to-face treatment (15).

Promising feasibility trial
We recently completed a feasibility trial at Karolinska Institutet, Sweden (NCT04511286), where we found that an internet-delivered flexible exposure-based treatment for individuals with high levels of symptom preoccupation regardless of somatic symptom domain (N=33; e.g., functional gastrointestinal symptoms, atrial fibrillation, migraine) can be delivered with high treatment adherence, adequate client satisfaction, large and lasting improvement in self-reported somatic symptoms and symptom preoccupation, and no serious adverse events. It is thus motivated to evaluate this treatment format further.

Need for a randomized controlled trial in a routine clinical setting
In further evaluating the flexible exposure-based treatment approach for patients with distress related to somatic symptoms it is imperative to conduct a randomized controlled trial versus an informative control condition, focusing on effects on somatic symptoms and symptom preoccupation. It is also important to evaluate if the treatment can be effective in a routine clinical setting and when patients are referred via a clinician such as a general practitioner.

Aim of the clinical trial

This trial aims to evaluate if flexible internet-delivered exposure-based treatment is more effective than an internet-delivered standardized routine care education program for patients with distress related to somatic symptoms in primary care.

Primary research question

- Compared to the control condition, does flexible internet-delivered exposure-based treatment lead to a larger improvement in self-rated somatic symptom burden as assessed using the Patient Health Questionnaire 15 (PHQ-15)? Hypothesis: Yes.

Key secondary research questions

- Compared to the control condition, does flexible internet-delivered exposure-based treatment lead to a larger improvement in symptom preoccupation, psychiatric symptom burden, and functional impairment? Hypothesis: Yes.

- In flexible internet-delivered exposure-based treatment, are effects maintained up to 12 months after treatment? Hypothesis: Yes.

- Is flexible internet-delivered exposure-based treatment cost-effective compared to the control condition? Hypothesis: Yes.

- Is the controlled effect of the flexible exposure-based treatment on self-rated somatic symptoms moderated by baseline symptoms and preoccupation? Hypothesis: Yes.

- Is the effect of the flexible exposure-based treatment on self-rated somatic symptom burden mediated by a reduction in symptom preoccupation? Hypothesis: Yes.

Methods

Design and power

Randomized controlled trial of flexible internet-delivered exposure-based treatment for distress related to somatic symptoms, based at Liljeholmen academic primary care clinic, Stockholm, Sweden. Patients (N=160) who report being bothered by somatic symptoms (and who may or may not meet criteria for a diagnosis where distress related to symptoms is common, such as fibromyalgia or asthma), who express interest in psychological treatment, and who's medical status does not make exposure therapy unsuitable are randomized (1:1), in consecutive even numbered cohorts, to flexible internet-delivered exposure-based treatment or an internet-delivered standardized education control. The trial is powered to enable the study of moderate between-group effects (d=0.5) as based on mean tests with 80% power, given alpha=0.05 and up to 20% data loss.

Eligibility criteria

a) (i) Either much bothered by at least one somatic symptom (2 points on at least one item of the PHQ-15) or at least a moderate overall somatic symptom burden (PHQ-15 sum 10 points (16)), with (ii) recurrent distress related to somatic symptoms ≥4 months
b) Symptoms not best explained by, and clinical picture not dominated by, severe health anxiety (where an established treatment already exists (17)) or a non-somatoform psychiatric disorder such as depression, panic disorder, primary insomnia, or a chronic stress disorder
c) Affirms that he or she is interested in completing an intense psychological treatment with the aim of reducing distress associated with physical symptoms
d) Adult (≥18 years old)
e) Living in Stockholm County
f) Can read and write in Swedish
g) Not severe psychiatric condition or suicidal ideation

h) No clear medical risk in taking part in exposure-based treatment (e.g., pregnancy) and somatic condition, or treatment for somatic condition, does not make treatment unfeasible
i) Continuous psychotropic medication (antidepressants, anticonvulsants, mood-stabilizers, antipsychotics) either non-existent or stable since at least 4 weeks, and expected to remain stable over the main phase of the trial
j) Not severe alcohol or substance use disorder likely to interfere with treatment
k) Not planned absence for more than 1 week during the intended main phase
l) Complete pre-treatment assessment

Instruments
Psychiatric assessment is based on the Mini-International Neuropsychiatric Interview (MINI (18)) and Health Preoccupation Diagnostic Interview (HPDI (19)). Primary outcome measure is somatic symptom burden as assessed using the Patient Health Questionnaire 15 (PHQ-15 (16)). Secondary outcomes are: symptom preoccupation (SSD-12 (20); SYMPS-prel), general anxiety (GAD-7 (21)), depression (PHQ-9 (22)), disability (WHODAS 2 (23)), credibility and expectancy (C/E scale (24)), relation with the therapist (WAI-6, (25)), client satisfaction (CSQ-8 (26)), negative effects (free-text questions), quality of life (EQ-5D (27)), and societal resource use (TIC-P (28)). Health anxiety (HAI-14, (29)) and alcohol/drug use (AUDIT, DUDIT (30, 31)) are assessed for the purpose of screening only. Eleven questions concerning the basis of subjective somatic symptom burden in terms of symptom severity, disability, and emotional components will also be administered at baseline so as to facilitate the interpretation of the PHQ-15.

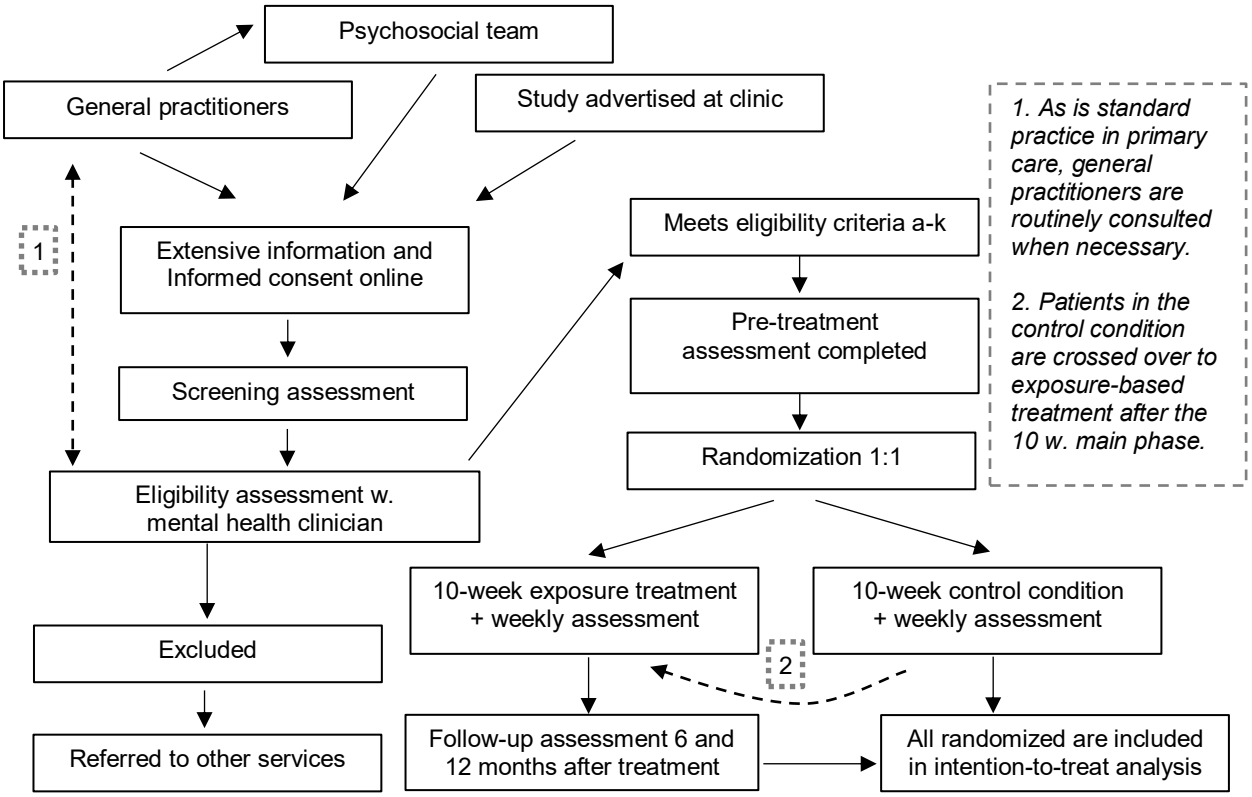

Figure 1. Schematic overview of participant flow

Procedure
We aim to recruit Swedish adults with recurrent distress related to somatic symptoms and an interest in psychological treatment. Patients will be referred via regular services including

general practitioners, the psychosocial team, and waiting room advertisement at Liljeholmen primary care clinic in southern Stockholm (Figure 1). If the rate of inclusion is too slow, patients will also be referred from other clinics of Stockholm, and, if necessary, based on newspaper and social media advertisement. Those interested in the trial are referred to the study website where they are given extensive information about the trial and contact information for the principal investigator. The data management plan is described in sufficient detail, and it is made clear that participants of the trial retain their right to take part in routine care services, and also to cancel their participation at any point without further justification. Visitors of the website are then given the option of providing informed consent via an encrypted online form, prior to which no information is collected. This is a common and secure method of providing informed consent, see for example EPM id 2020-01740.

Once informed consent has been provided, the applicant is granted a personal account on the secure online measurement platform and is prompted to provide data on identity and sociodemographic variables including age, gender, and educational attainment. Then follows a series of self-report questionnaires and questions about key clinical variables including medications, diagnoses, and prior treatment. The purpose of this screening assessment ("SN" in Table 1) is to collect sufficient data to ensure reliable assessment of eligibility criteria (above) and enable adequate description of the sample.

After having completed the screening, applicants are contacted for a psychiatric assessment (primarily the MINI) and eligibility interview with a mental health clinician. As is routine practice at the clinic, this may be conducted face-to-face, via telephone, or via a secure video conferencing service. As is routinely done in the primary care clinic, the patient's general practitioner is consulted whenever further medical evaluation is deemed necessary. Applicants who do not meet eligibility criteria a-k are excluded and referred to routine care, at the clinic if possible, and in accordance with regional healthcare guidelines. Applicants who meet eligibility criteria a-k are encouraged to complete the pre-treatment assessment. Those who do so are randomized (1:1) to flexible internet-delivered exposure-based treatment or the education control and are thereby included as participants in the trial. The subsequent 10 weeks constitute the main phase of the trial during which key measures are administered on a weekly basis (Table 1). At the end of the main phase follows the post-treatment assessment. Follow-up assessments follow 6 and 12 months after therapy.

Table 1. Key outcome measures and assessment points

Questionnaire	Outcome	Reference	SN	PRE	WK	POST	6MFU	12MFU
PHQ-15 (prim.)	Somatic symptoms	(16)	x	x	x	x	x	x
SSD-12	Symptom preoccupation	(20)	x	x	x	x	x	x
SYMPS-prel	Symptom preoccupation	Prel. version	x	x	x	x	x	x
GAD-7	Anxiety	(21)		x		x	x	x
PHQ-9 [a]	Depression	(22)	x	x		x	x	x
WHODAS 2.0	Disability	(23)	x	x		x	x	x
HAI-14	Health anxiety	(29)	x					
AUDIT, DUDIT	Alcohol, drug use	(30, 31)	x					
C/E scale	Credibility/expectancy	(24)			w. 3			
WAI-6	Relationship w. therapist	(25)			w. 3			
CSQ-8	Client satisfaction	(26)				x		
EQ-5D	Health-rel. quality of life	(27)		x		x	x	x
TIC-P	Resource use	(28)		x		x	x	x

12MFU = 12-month follow-up, 6MFU = 6-month follow-up, POST = post-treatment, PRE = pre-treatment (i.e., end of main phase), SN = screening, WK = weekly assessment (main phase week 1-9)
a) Suicidality item administered each week; patients contacted if flagged and referred to routine care as needed.

Data management

Data are stored on secure servers and managed in accordance with Swedish and European data protection and privacy legislation. Treatment is provided via the routine care online treatment platform of Region Stockholm ("Stöd- och behandlingsplattformen", SOB) which requires electronic identification and relies on encrypted traffic. Electronic records are also kept in a secure data system, as is required by law, and in accordance with SLSO guidelines. For the purpose of this study, a separate online measurement platform is used, with data stored on secure servers managed by Karolinska Institutet on behalf of Liljeholmen primary care clinic ("personuppgiftsbiträdesavtal"). This measurement platform has been used in several previous clinical trials of internet-delivered treatment, see for example EPM ethics applications 2019-04816 and 2020-01740. All trial applicants are required to log in to the measurement platform with electronic identification, and subsequent communication relies on encrypted traffic and two-factor authentication (a personal password + unique SMS codes).

Clinicians who deliver treatments in the context of this trial are only permitted access to those online treatments for which they are responsible. Likewise, on the measurement platform, patients' weekly measurements of somatic symptoms and symptom preoccupation can be monitored by each respective therapist so as to facilitate conventional adaptation of clinical interventions (as is done in routine care), but the extraction of outcome data for the purpose of research (all of Table 1, all participants) is only made available for researchers of the trial and one research assistant. All datasets are pseudonymized by means of a built-in function on the measurement platform, stored on secure servers, and not together with information that allows for individuals to be re-identified. Such information ("kodnyckeln") is stored separately, exclusively in encrypted form, and is solely accessed by the researchers and the assistant of the trial. Results are published and conveyed in a way that does not allow for the identification of any participant. In accordance with SLSO guidelines, 10 years after the last publication, original datasets and information necessary for individuals to be identified ("kodnyckeln") are deleted and key documentation from the trial is transferred to long-term storage in the Region Stockholm archive.

Conditions

Both conditions involve structured content that is delivered via the secure routine care text-based treatment platform (SOB, see above) over the 10-week main phase. In both conditions, patients are given a personal account to the SOB to which they may log in at any time.

Flexible internet-delivered exposure-based treatment

The flexible exposure-based treatment protocol was written by Erland Axelsson for a previous feasibility trial at Karolinska Institutet, Stockholm, Sweden (ClinicalTrials.gov identifier NCT04511286). In this treatment, the patient completes the equivalent of 5 book chapters with homework exercises, and communicates with a therapist via an email-like system. The therapist is either a licensed psychologist or a mental health clinican with adequate training in psychotherapy under supervision that replies to messages from the patient within 48 hours except during weekends. Exposure exercises are tailored to the needs of the particular patient. The initial phase of treatment incorporates education about how psychological factors can contribute to somatic symptom distress, functional impairment, and overall symptom burden. The patient is encouraged to survey his or her own reactions to physical symptoms and attempt to refrain from strategies aimed at short-term reduction in symptoms and related distress (response prevention). The following modules encourage the patient to work with tailor-made exposure exercises in various ways. The treatment is thus similar to several previously evaluated protocols intended specifically for functional somatic syndromes

including fibromyalgia (4) and irritable bowel syndrome (5) or chronic health conditions such as asthma (3) and atrial fibrillation (12).

Standardized routine care education and prolonged assessment control
Patients randomized to the standardized education and prolonged assessment condition are provided with standardized routine care educational material about the management of psychological distress and somatic symptoms, as available via the national 1177.se service. Via email-like messages on the treatment platform, patients also receive basic emotional support by a clinician who encourages the patient to (1) adhere to standardized routine care guidelines for the management of distress and symptoms, (2) make use of regular health care services, and (3) monitor symptoms and wellbeing on a weekly basis. After the post-treatment assessment, participants in the control condition are crossed over to the tailored exposure-based treatment. In other words, all participants of the randomized controlled trial are offered to take part in exposure-based treatment for distress related to somatic symptoms.

As to the choice of control condition, it is important to recognize that while there exists no standout reference standard treatment for patients with distress related to somatic symptoms, the most common practice in primary care is probably that of offering support and promoting healthy lifestyle behaviors such as physical exercise, a healthy diet, and regular recuperating behaviors (8, 32). We thus expect the standardized routine care education and prolonged assessment control to produce effects similar to those typically resulting from support given in routine care, for example by the individual general practitioner.

Statistical analysis
The analysis plan here described will be pre-registered as part of this study protocol. Multiple imputation will be based on the following predictors: time, age, gender, screening somatic symptoms, screening symptom preoccupation, treatment adherence, and missing data rate. This will be done separately for each condition (exposure vs. control) so as to maintain group-specific interactions. Change in the primary outcome measure (PHQ-15) and other continuous scales will be analyzed using multilevel regression models (33) with patient at level 2, using an autoregressive (AR(1)) covariance structure, fitted by maximum likelihood. Longitudinal outcomes will be modelled intention-to-treat, with time, group (exposure vs. control), and the time×group interaction as predictors (α=5%). As the feasibility trial was indicative of a curvilinear effect of time (unusual in the field), the inclusion of a time×time interaction will also be considered based on model fit. The primary statistical test is that of the coefficient for the time×group interaction pertaining to a group difference in average change in the PHQ-15 over the main phase of the trial, i.e., from pre- to post-treatment. Standardized mean effects are conceptualized as the time×group interaction divided by the endpoint standard deviation. Long-term effectiveness is modeled using piecewise regression models, with a spline at post-treatment. Response rates are also explored in terms of clinically significant change (34). The following putative moderators will be explored based on time×group×moderator interactions: age, gender (if adequate power), screening somatic symptoms, and screening symptom preoccupation. Explorative secondary analyses will also focus on change in each somatic symptom domain of the PHQ-15 (pain, gastrointestinal, cardio-pulmonary, fatigue) as well as specific functional somatic syndromes and chronic health conditions if the number of patients in each condition is at least 5. Cost-effectiveness analysis is based on the incremental cost-effectiveness ratio (ICER) and focuses on a societal perspective, with resource use derived from the TIC-P and sensitivity analyses based on cluster bootstrapping (35). Mediation analysis is based on latent growth modelling (36), and random-intercepts cross-lagged panel models (37) to assess temporal superiority, i.e., whether change in putative mediators

systematically precede change in outcomes on a week-by-week basis. We will also test the hypothesis that men are more inclined than women to seek health care for somatic symptoms when they are in fact suffering from a psychiatric condition, as based on a 2x2 $\chi 2$ test of exclusions due to other principal psychiatric conditions vs. other factors, men vs. women.

Time schedule as of February 2021

After approval from the Swedish Ethical Review Authority this project is scheduled to be completed in approximately 3 years, beginning with the education of personnel over the first half of 2021. Recruitment is expected to begin around the summer of 2021. We expect to recruit approximately 50-80 patients per year, which implies that recruitment will be complete around the middle of 2023. We expect the last follow-up assessment, and writing of the primary journal article to take place around mid-2024. Results will be communicated via peer reviewed scientific journal articles.

Research group

The researchers have conducted several clinical trials of psychological interventions in a primary care setting and are well familiar with somatic symptom and related disorders, functional somatic syndromes, and the preoccupation with physical symptoms. The principal investigator, **Erland Axelsson**, lic. psychologist, PhD, Liljeholmen primary care clinic and affiliated with Karolinska Institutet has published extensively in the field of somatic symptom and related disorders and been involved in more than 10 randomized clinical trials of psychological treatment, focusing primarily on musculoskeletal pain, chronic stress, anxiety, depression, and atrial fibrillation. He has certification in good clinical practice (GCP), has led the largest published direct comparison of internet-delivered and face-to-face treatment for any psychiatric condition, and has several years of experience in evaluating interventions, supervising clinicians, developing research methods, and overseeing the daily management of clinical trials in a primary care context. **Sandra af Winklerfelt Hammarberg**, lic. physician and general practitioner, PhD student at Karolinska Institutet and head of Liljeholmen primary care clinic has extensive experience of clinical work in primary care and expertise in research on mental health interventions. **Brjánn Ljótsson**, lic. psychologist, associate professor and research group leader at Karolinska Institutet. Brjánn co-founded the Internet psychiatry unit of Region Stockholm and has developed an internationally recognized exposure-based treatment protocol for irritable bowel syndrome. Brjánn is a world leading researcher in the field of psychological treatment for functional somatic syndromes and certain somatic conditions such as atrial fibrillation. **Eva Toth-Pal**, lic. physician and general practitioner, PhD, research coordinator at Liljeholmen primary care clinic and affiliated with Karolinska Institutet. Eva has extensive experience of clinical work in primary care and specializes in research in the primary care context.

Ethical considerations

This trial is to be conducted in accordance with the declaration of Helsinki and the ethical guidelines of the Swedish Research Council. Patients who are frequently preoccupied with physical symptoms tend to report high levels of psychiatric comorbidity and substantially lowered quality of life. It is thus important not to cause additional suffering or negative consequences as a result of participation in this study. Based on previous research, we expect a 20-40% risk of adverse events, but these are likely to be relatively mild, transient, and of expected quality (typically a short-term increase in symptoms). No serious adverse events in terms of death, serious injury or deterioration requiring hospitalization has been reported in previous studies of similar interventions which implies that such outcomes are deemed highly

unlikely also in the present project. Suicidal ideation is monitored on a weekly basis, patients are given access to an online platform where they have the possibility of contacting a clinician, and negative events are reported extensively at the post-treatment assessment as well as briefly on a weekly basis over the main phase of the trial. Patients who express suicidal ideation or adverse events that affect them at least to a moderate degree are flagged in the measurement platform, and then contacted by a mental health clinician via telephone for an individual clinical assessment based on which a decision is made to offer or refer the patient to additional services, and whether it is necessary to terminate the intervention prematurely.

Some patients will be randomized to the control condition which is likely to be less efficacious than the exposure-based treatment. However, we expect the control condition to be about as effective as a typical intervention offered for the patient group in routine care. We also expect the control condition to lead to no or very few adverse events. Patients in the control condition are crossed over to exposure-based treatment after the main phase of the trial. Thus, all participants of the study are offered to take part in the exposure-based treatment, the equivalent of which is very rarely offered in routine care. Another risk factor is the possibility of a data breach. We consider this risk small, considering that all data is stored on secure servers and is accessed by the researchers only (see “Data management”).

In summary, we consider the potential scientific value of the trial combined with the potential gains for individual participants to clearly outweigh the potential harms of the project. Not least, we wish to highlight that distress related to somatic symptoms is a highly prevalent problem that is often seen in routine care, but which often goes unaddressed. Serious adverse events are deemed unlikely and are also surveyed on a weekly basis. The procedure to prevent data breach is also deemed adequate to ensure the safety and wellbeing of all patients.

Clinical implications

This is the first randomized controlled trial of exposure-based treatment for distress related to somatic symptoms where participants are not selected based on having any particular functional somatic disorder or particular disease. Little is known about the effectiveness, cost-effectiveness, and putative mechanisms of a flexible exposure-based intervention of the kind evaluated here. Exposure-based treatment that can be adapted to suit a broad spectrum of groups could potentially improve access to adequate care for many groups suffering from distress related to somatic symptoms in primary care which is tasked with treatment for mild to moderate mental health problems in Sweden. This is also one of few randomized controlled trials of online therapy in Scandinavian routine care; of clinical significance for the transition to digital care that has accelerated since beginning of the covid-19-pandemic. Considering that the treatment can be administered online, it can be offered also to patients living in rural areas where specialist clinics are few and reduce the impact on stigma on health care seeking. In summary, the exposure-based treatment evaluated here has the potential to radically improve access to effective treatment for this large and often overlooked patient group.

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