Study protocol

Exposure-based treatment for undifferentiated somatic symptom disorder

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Note that due to the feasibility nature of this clinical trial, there was no statistical analysis plan over and above the rudimentary a priori guidelines for interpretation listed in Table 1.

Approved by the Swedish ethical review authority on May 20th 2020.

Translated to English on July 19th 2021.

Study protocol

Exposure-based treatment for undifferentiated somatic symptom disorder: a feasibility study

Summary
A substantial proportion of patients in the health care system are bothered by a recurrent preoccupation with physical symptoms. Whenever this preoccupation becomes clinically significant in terms of cognitions, emotions or behaviour and cannot be explained by the common anxiety or mood disorders, the criteria for DSM-5 somatic symptom disorder are likely to be met. Exposure-based psychological treatment where the patient systematically seeks out situations that give rise to symptoms and related discomfort have been found to have meaningful effects on subjective somatic symptom burden and mood in several forms of preoccupation with physical symptoms, but is rarely offered in routine care, probably partially because existing treatment protocols have been developed for specific somatic symptom clusters (e.g., fibromyalgia) or specific forms of preoccupation with symptoms (e.g., the fear of having or developing a severe disease). The aim of this study is to investigate the feasibility of offering exposure treatment for somatic symptom disorder without selecting patients based on their specific somatic symptoms or most pronounced emotional reaction to somatic symptoms. Instead, the treatment is expected to be suitable for many types of preoccupation with symptoms, and many forms of physical symptoms, which potentially makes the protocol relevant for a wider target group. A within-group feasibility trial is conducted at Karolinska Institutet, where 40 participants with somatic symptom disorder are enrolled in psychological treatment for 8 weeks. The outcome of the study focuses on various aspects of feasibility.

Overview of the field *(background)*
One fifth of primary care patients, and approximately 37-66 percent of specialist care patients, seek care for symptoms without a clear medical explanation (1-3). Many of these patients are diagnosed with a functional somatic syndrome; a diagnosis primarily based on the presence of physical symptoms such as fibromyalgia in rheumatology or irritable bowel syndrome in gastroenterology (4). Such conditions commonly lead to considerable suffering and functional impairment (5, 6), and put substantial strain on the health care system (7). Pharmacological therapies, typically antidepressants and symptom-specific medications, often do not provide adequate relief (8).

Somatic symptom disorder is a diagnosis characterised by a clinically significant pattern of negative interpretations, anxiety or excessive health behaviours in relation to somatic symptoms. This type of preoccupation with symptoms affects the experience and intensity of a large number of physical symptoms, both with and without a clearly defined medical genesis (9). For example, in pain, the fear and preoccupation with pain has been found to have a higher predictive value for chronicity than pain itself (10). Behaviours that serve to evaluate somatic symptoms, seek information about symptoms and avoid symptom-related discomfort often contribute to impaired functioning and worsened symptoms in the long term (11-13).

In exposure-based treatment, the patient is encouraged to reduce his or her preoccupation with somatic symptoms by systematically seeking out and approaching situations and phenomena that give rise to unwanted somatic symptoms or symptom-related discomfort. The treatment is

[Translated from the original that was approved by the Swedish ethical review authority] tailored for the needs of the patient as based on functional analysis. This type of treatment has been found to be efficacious in several functional somatic syndromes, such as fibromyalgia and irritable bowel syndrome (14, 15), as well as in specific types of symptom preoccupation such as health anxiety and anxiety sensitivity (16, 17). In clinical trials where patients have been recruited based on a specific syndrome or class of somatic symptoms, the primary outcome has typically focused on subjective somatic burden, and within-group effects have been typically moderate to large.

In Swedish healthcare, access to exposure-based treatment for somatic symptom disorder is poor. Only about every other primary care clinic reports being able to meet patients' demand for mental health care (18), and primary care often lacks the necessary resources for offering specific psychological treatments for functional somatic syndromes and specific forms of preoccupation with somatic symptoms. A unified treatment protocol that could suit a wider spectrum of physical symptoms and types of preoccupation with somatic symptoms could potentially increase access to exposure-based treatment for somatic symptom disorder. However, it is yet unclear if one and the same exposure-based treatment could be rated as credible and be sufficiently effective for the heterogeneous group of individuals who seek care for somatic symptom disorder, regardless of symptom domain (e.g., fibromyalgia) or type of preoccupation with symptoms (e.g., health anxiety).

Research question (study aims)

The aim of this within-group study is to evaluate an exposure-based treatment for somatic symptom disorder in terms of credibility and feasibility (see Table 1). Secondary outcomes include preliminary within-group efficacy, where the expectation is at least a moderate effect (ca d=0.5) on subjective somatic symptom burden (see Table 2).

Table 1. Dimensions of feasibility assessed within the study

Feasibility aspect	**Outcome**	**A priori rule of thumb for adequacy**
Distribution of somatic symptoms and preoccupation with symptoms	See Table 2	Exploratory, interpreted in the light of other aspects such as recruitment path (proportion of patients informed of the study by a health care provider)
Treatment credibility	Credibility/Expectancy scale (19)	Mean of at least ca 30 points (equivalent to a mean of 6 on a scale from 0 to 10)
Adherence to the protocol	Number of completed modules Number of completed exposure exercises	At least ca 60% of modules completed At least ca 50% of participants having worked actively with exposure (at least 2 exposure exercises)
Credible rationale for exposure	Study-specific Likert-scale (mid- and post-treatment) [Note: This was only administered at post.]	-
Weekly measurements of somatic symptom burden and symptom preoccupation	Number of measurements completed Perceived strain caused by measurement strategy	Post-treatment data retention ca 70% At least 75% regard the strain to be acceptable [Note: Below 7 on a scale from 0 to 10, as decided on Nov 13th.]
Satisfaction with the treatment	Client Satisfaction Questionnaire (CSQ-8) Modified questionnaire from Swedish ethical review authority application 2019-03317 [Note: Not	CSQ-8 mean of at least ca 22 points

	administered due to an administrative error.]	
Adverse events and negative experiences	Adverse events questionnaire used in previous clinical trials (e.g., Regional ethics review board of Stockholm application 2014/1530-31), NEQ-20	Exploratory, weighed against preliminary efficacy

Description of the research project (methods)

Design
Observational study at Karolinska Institutet [Note: Stockholm, Sweden]. Frothy participants with somatic symptom disorder are recruited via information to primary care, the study web page and advertisements in social media, and are subsequently offered 8 weeks of exposure-based treatment via the internet. Recruitment is scheduled to begin in mid-August 2020.

Recruitment
The target group is adult swedes with somatic symptom disorder who are interested in psychological treatment. Recruitment is conducted via information to health care clinics, the study webpage and social media advertisements. Individuals expressing interest in the study are referred to the study web page where they are encouraged to submit an application. The self-referral procedure ensures that these individuals are given time to reflect on their decision to apply for the study. At the time of application, the potential participant is immediately presented with the information necessary for informed consent. The voluntary nature of participation, routines for the management of data and the risks of participation are conveyed in a clear manner. Informed consent is provided via the web platform, which is a method used in previous clinical trials, see for example Regional ethics review board of Stockholm applications 2013/375-31/5 and 2014/1530-31. An interview with a licensed psychologist or trainee psychologist under the supervision of a licensed psychologist is conducted via telephone for the collection of routine clinical data and the assessment of eligibility criteria:

a) DSM-5 somatic symptom disorder as assessed using the Health Preoccupation Diagnostic Interview (HPDI) (20), with at least 4 months of recurrent somatic symptoms
b) The preoccupation with somatic symptoms is not better explained by another psychiatric disorder such as illness anxiety disorder, panic disorder or obsessive-compulsive disorder
c) The individual reports being interested in undergoing a focused psychological treatment for 8 weeks, to reduce the impact of bothering physical symptoms
d) At least 18 years old
e) Swedish citizen living in Sweden
f) Can speak and read Swedish
g) No severe psychiatric condition such as bipolar disorder, suicidal ideation or a psychotic disorder. This is based on the eligibility interview where the clinician administers the Mini-International Neuropsychiatric Interview (MINI) (21).

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h) Not obvious medical risks associated with exposure-based treatment, and no somatic condition, or treatment for a somatic condition, is a significant obstacle for exposure-based treatment.
i) Continuous psychotropic medication (e.g., antidepressants, anticonvulsants, benzodiazepines, nonbenzodiazepines) and medication with opioids has been stable for the past 4 weeks and is expected to remain so during the intended treatment period.
j) Not alcohol or substance use deemed a serious obstacle to taking part in therapy
k) Not planned absence for more than one week of the intended treatment period
l) Complete pre-treatment assessment

Treatment

Patients complete an 8-week exposure-based treatment. The treatment is a text-based guided self-help intervention provided via the internet (22), with five modules, equivalent to book chapters, with corresponding exercises alongside email-like communication with a therapist. The treatment manual, written by Erland Axelsson, is made freely available via the internet.

The treatment is tailored to suit the unique needs of each patient. The introduction of the treatment (module 1) focuses primarily on education about how psychological factors can contribute to somatic symptoms and related problems. The patient begins to monitor his or her own behavioural patterns in relation to somatic symptoms and begins working with response prevention (23), that is, the reduction of behaviours aiming to reduce symptoms and related discomfort in the short term. During the following modules, the patient plans individually-tailored exposure exercises that are expected to give rise to discomfort related to physical symptoms including unwanted thoughts. The treatment is delivered by a licensed psychologist or trainee psychologist under supervision.

Measurements and psychometric instruments

Measurements primarily rely on self-report questionnaires administered via a secure web platform (encrypted traffic and two-factor authentication). The study involves the following measurements: the screening (at application), the pre-treatment assessment (before week 1), weekly measurements during the treatment period (before week 2-8) and the post-treatment (after week 8). A follow-up assessment is also conducted 3 months after treatment. Automatic SMS reminders prompt participants to complete each measurement, and manual reminders are given via telephone if necessary, without conveying treatment content. Over and above routine clinical questions for example regarding sociodemographic variables (such as age, sex, educational attainment and civil status) the following questionnaires are administered via the internet:

Table 2. Self-report questionnaires administered in the study

Questionnaire	Outcome	Ref	SN	PRE	W	POST	3MFU
Patient Health Questionnaire-15 (PHQ-15)	Somatic symptom burden	(24)	x	x	x	x	x
Somatic Symptom Disorder-B Criteria Scale (SSD-12)	Symptom preoccupation	(25)	x	x	x	x	x
Symptom Preoccupation Scale (SYMPS-prel)	Symptom preoccupation	Preliminary version	x	x	x	x	x
14-item Health Anxiety Inventory (HAI-14)	Health anxiety	(26)	x	x		x	x
Anxiety Sensitivity Index (ASI)	Anxiety sensitivity	(27)	x	x		x	x

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GAD-7	Anxiety (general)	(28)		x		x	x
Patient Health Questionnare (PHQ-9) [a]	Depression	(29)	x	x		x	x
12-item WHO Disability Assessment Schedule 2.0 (WHODAS 2.0)	Functional impairment	(30)	x	x		x	x
Alcohol Use Disorders Identification Test (AUDIT)	Alcohol use	(31)	x				
Drug Use Disorders Identification Test (DUDIT)	Drug use	(32)	x				
Credibility/Expectancy scale (C/E scale)	Credibility and expectancy	(19)			w. 3		
Working Alliance Inventory (WAI)	Relationship with the therapist	(33)			w. 3		
Client satisfaction questionnaire (CSQ-8)	Satisfaction with the treatment	(34)				x	
20-item Negative Effects Questionnaire (NEQ-20)	Negative experiences	(35)				x	

3MFU = 3-months follow-up, PRE = pre-treatment, POST = post-treatment, SN = screening, W = weekly

a) The suicidal ideation item is administered on a weekly basis. Patients with heightened scores are contacted and referred to routine care if deemed necessary.

Data safety and management

The study web platform employs encrypted traffic and two-factor authentication. Researchers in the project have access to study data, which is stored and managed in accordance with European Union and Swedish data protection and privacy legislation. Personal data are exclusively stored in systems classified and provided specifically for this purpose by Karolinska Institutet. Study results are reported in a manner that does not make it possible to identify individual participants.

Time schedule and feasibility

Recruitment for the study is scheduled to begin in August 2020. Eligibility interviews are conducted in September 2020, treatments span from October to December 2020 and a follow-up assessment is conducted 3 months after treatment termination with some tolerance for late replies. Data collection is expected to end around May 2021. The processing of data is expected to be relatively swift, and a scientific manuscript is expected to be submitted for peer review around June 2021, thus probably reaching publication in the autumn of 2021.

Researchers in the project have extensive experience of conducting clinical trials of psychological treatment via the internet, and in particular for groups similar to that studied in the present study – e.g., individuals with health anxiety and irritable bowel syndrome – and with similar recruitment strategies. The treatment evaluated in this research project is intended to meet a large and seemingly unmet need in the population, and the study has been approved by the head of the Department of clinical neuroscience at Karolinska Institutet, which speaks for the study being completed as planned.

The research group

The researchers have extensive experience of research in primary care and concerning psychological treatment for somatoform conditions, functional somatic syndromes and anxiety related to somatic conditions. **Erland Axelsson**, licensed psychologist and PhD at Karolinska Institutet, wrote his dissertation on the exposure-based treatment of health anxiety,

a form of preoccupation with symptoms, and has developed a diagnostic interview for the assessment of somatic symptom disorder. Erland has made contributions to several clinical trials of psychological treatment for conditions such as fibromyalgia, chronic stress disorders, pathological worry, depression and paroxysmal atrial fibrillation. Erland has documented experience of the development and evaluation of psychological treatments including study design, the implementation of research methods, the supervision of clinicians and the day-to-day project management of clinical trials in primary care. **Brjánn Ljótsson**, licensed psychologist and PhD, associate professor, is a research group leader at Karolinska Institutet. Brjánn co-founded the Internet psychiatry unit of Region Stockholm and has led the development of several internationally recognised exposure-based protocols for individuals reporting distress related to somatic symptoms. Brjánn is a world-leading researcher in psychological treatment for functional somatic syndromes, specialising in irritable bowel syndrome and certain somatic conditions such as atrial fibrillation. Brjánn has also taken part in treatment research at Gustavsberg academic primary care clinic. **Sandra af Winklerfelt Hammarberg** licensed general practitioner and doctoral student at Karolinska Institutet is the head of Liljeholmen academic primary care clinic, Stockholm, Sweden. Sandra has extensive experience of clinical work in primary care and has expressed interest in supporting the project. **Robert Johansson** licenced psychologist and PhD, associate professor at Stockholm university, has extensive experience of clinical research focusing on anxiety and mood disorders. Robert is heading a research program for the development and evaluation of emotional awareness and expression therapy (EAET) for somatic symptom disorder.

Significance

A credible and promising exposure-based treatment for undifferentiated somatic symptom disorder could potentially lead to a significant improvement in the access to treatment for patients with somatic symptom disorder in primary care. If results are found to be promising, the next step could be to assess treatment efficacy more carefully, for example versus standard interventions (“usual care”) within the context of a randomised controlled trial in routine care.

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