PROTOCOL

Internet-delivered psychological treatment of functional gastrointestinal disorders - A Danish feasibility study

A study embedded in The Danish FGID treatment study

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1. Original title

Internet-delivered psychological treatment of functional gastrointestinal disorders (FGID) - A Danish feasibility study. A study embedded in The Danish FGID treatment study.

2. Aim and rationale for the study

a. Aim: To test the feasibility of an exposure-based internet-based cognitive behavioral therapy (I-CBT) treatment not previously evaluated in Denmark for adults with FGID in a Danish clinical context.

b. Method: 30 adults with FGID will complete an exposure-based I-CBT treatment not previously evaluated in Denmark for adults with FGID, that has been translated and adapted from Swedish into Danish. The feasibility and potential effect will be assessed via treatment completion, satisfaction with treatment, abdominal symptoms and quality of life.

Hypothesis: The feasibility of the I-CBT program will be assessed positively by the patients. At least 70% of included patients will complete the treatment. Furthermore, the I-CBT program will reduce symptoms of FGID and increase quality of life in patients with FGID.

d. Literature: Functional gastrointestinal disorders (FGID) are characterized by recurrent abdominal pain and change in defecation patterns and consistency, nausea, bloating and flatulence, which cannot be explained by other somatic or psychiatric disease. The disorders are common in the general population and are associated with negative outcomes such as functional disability, high health care use, lowered quality of life, and absence from work, as well as psychiatric co-morbidity particularly with anxiety and depression (e.g., Ford, Lacy, & Talley, 2017; Petersen et al., 2020; Schmulson & Drossman, 2017; Van Oudenhove et al., 2016). The most common sub-type is irritable bowel syndrome (IBS), which has an estimated prevalence of 11% in adult populations (Lovell & Ford, 2012; Schmulson & Drossman, 2017).

FGID are suggested to be influenced by psychosocial factors and altered physiology via the brain-gut axis (Ford et al., 2017; Schmulson & Drossman, 2017), hence it is argued that FGID are best understood within a biopsychosocial framework (e.g., Kinsinger, 2017; Van Oudenhove et al., 2016). This could be one of the reasons why there is only weak support for the effect of medical or dietary treatment, whereas psychological interventions like cognitive behavioral therapy (CBT) have shown large and long-term effects in patients with FGID (for a review, see Kinsinger, 2017). In Sweden, a group of experts have developed an internet delivered CBT (i-CBT) program for adults with FGID. The program includes psychoeducation about FGID and specific focus on exposure-based methods to target avoidance and control behaviors. The program has shown very promising effects in several studies among self-referred patients (Ljótsson 2010, 2011, 2014), and further has the advantage that i-CBT is more flexible and less costly than traditional CBT treatment, and can therefore better meet the high needs for availability and accessibility to specialized treatment (Kinsinger, 2017).

3. Methods

This is a feasibility study testing a of an exposure-based I-CBT treatment for FGID not previously evaluated in Denmark.

a. Data collection and outcome measures

After informed consent has been obtained, , patients are invited for a psychiatric screening interview performed by a psychologist with specialty in functional disorders to ensure inclusion and exclusion criteria, specifically that no psychiatric disease is primary. Before the psychiatric screening interview, the patient completes a short questionnaire (time 0)via the secure web-based software platform for data collection Research Electronic Data Capture (REDCap; Harris et al., 2009, 2019) hosted at Aarhus University on physical symptoms, health anxiety, illness perception, and symptoms of anxiety and depression. The psychologist uses this information to prepare for the screening interview. These data will also be included in the project.

The questionnaires used are:

- Physical symptoms (BDS Checklist; Budtz-Lilly et al., 2015, 25 item)
- Illness worry (Whiteley index; Conradt et al., 2006; Fink et al., 1999, 6 items)
- Illness perceptions (3 items from Illness Perception Questionnaire; Broadbent et al., 2006)
- Symptoms of anxiety and depression (SCL Anxiety and Depression subscales; Christensen et al., 2005, Derogatis, 1983, 12 items)
- Nine Item Avoidant/Restrictive Food Intake disorder screen (NIAS), 9 items), Zickgrad & Ellis, 2018)

Additional measures consist of self-report measures (see table 1) obtained through REDCAP . Questionnaires will be administered at three time points: 1) Baseline, i.e. right after inclusion of patients; 2) End of treatment, i.e. after 10 weeks of treatment; and 3) 3-months follow up, i.e. 3 months after treatment.

As part of the questionnaire we will measure *Resting state cognition using the resting state paradigme: Patients are instructed to sit with their eyes closed for 3 minutes. Afterwards they answer questions in relation to what they thought and felt during the 3 minute period.* Additionally, during two distinct weeks — at the start and at the end of the treatment period — patients will receive a short questionnaire via SMS five times per day and be asked to complete it throughout each of these weeks.

The feasibility and acceptability of the program will be measured by the degree of treatment adherence, number of contacts with therapist, numbers of patients who are eligible and accepts to participate, as well as assessment of potential adverse effects of the treatment, self-assessed quality of the contact with the therapist, user satisfaction with the program, expectations for and perceptions of the treatment's credibility, and self-perceived effect of the treatment.

We will also measure potential treatment effects with the *severity of gastrointestinal symptoms and quality of life*, see Table 1 for details.

Other measures include symptoms, emotional distress, symptom-related concerns as well as maladaptive perceptions, behaviors and cognitions.

Table 1

Outcomes	Questionnaire	Number of items	Distribution time-point
Feasibility and acceptance measures			

Participants expectations and perception of the treatment's credibility	Expectation for counseling success (ECS; Kim et al., 2005)	6	1, 2
Evaluation of initial assessment	Single items	6	1
Evaluation of the treatment	Single items	8	2
Participants perception of the working alliance with the therapist	Working Alliance Inventory – Short Form (WAI-SF; Tracey & Kokotovic, 1989)	12	2
Side-effects of psychotherapy	Inventory for the balanced assessment of Negative Effects of Psychotherapy (INEP; Ladwig, Rief & Nestoriuc, 2014)	39	2
Evaluation of the internet program	(LEVA; In the process of finding the reference)	6	2
Primary measures			
Gastrointestinal symptoms	Gastrointestinal Symptom Rating Scale – Irritable Bowel Syndrome (GSRS-IBS; Wiklund et al. 2003)	20	1, 2, 3
Quality of life	Irritable Bowel Syndrome Quality of Life (IBS-QOL; Patrick et al., 1998)	34	1, 2, 3
Secondary measures			
Gastrointestinal symptoms	ROME IV	5	1, 3
Restrictive eating	NIAS	9	0, 3
Functional symptoms	Bodily Distress Syndrome Checklist (BDS Checklist; Budtz-Lilly et al., 2015)	25	0, 1, 2, 3
Illness behavior	IBS-Behavioral Responses Questionnaire	26	1,2,3
Illness perceptions	Illness Perception Questionnaire (IPQ; Broadbent et al., 2006, 2015)	21	0, 1, 2, 3
Illness concerns	Whiteley index (Conradt et al., 2006; Fink et al., 1999)	8	0, 1, 2, 3
Symptoms of anxiety and depression	Symptom Check List - Anxiety and Depression subscales (SCL-ANX & SCL-DEP; Christensen et al., 2005; Derogatis, 1983)	13	0, 1, 2, 3
Working hours and sick leave	Questionnaire on healthcare consumption and productivity losses for	10	1, 2, 3

	patients with a psychiatric disorder (TiC-P; Bouwmans et al., 2013)		
Spontaneous cognitions and feelings during rest	Amsterdam Resting State Questionnaire (ARSQ; Diaz et al., 2013, 2014)	58	1, 2, 3
Self-perceived change	Patient global impression of change (PGIC; Guy, 1976; Perrot & Lantéri-Minet, 2019)	1	2
Mind-wandering	Mind-wandering in daily life (Kane et al. 2007)	5	5 times a day for 2 weeks

b. The intervention

The i-CBT program consists of 5 modules and takes 10 weeks to complete. The participants will be expected to use approximately 4 hours per week on the treatment. Asynchronous written support will be provided by a therapist on a weekly basis. The therapists are experienced in CBT treatment and will receive regular supervision by the Swedish collaborators.

The treatment program consists of:

- Thorough information regarding FGID provided as text.
- Introduction to basic treatment principles of CBT provided as text.
- Exercises to help the patients become aware of their FGID symptoms and FGID-related thoughts in daily life.
- Exercises to help the patients discover what they have been avoiding due to their symptoms (e.g. specific foods, situations or activities).
- Exposure exercises to previously avoided foods, situations or activities.
- Advice on how to prevent relapse and maintain the treatment effect.

c. Deviations from standard care

The treatment offered in this study is a new and not currently available to patients with FGID as standard treatment.

4. Analysis and statistics

Data will be presented and analyzed according to current guidelines for feasibility studies (Lancaster & Thabane, 2019; Thabane et al., 2016). Traditional power and sample size considerations are not applicable for a feasibility study, but the number of participants is similar to other published non-randomized feasibility studies (e.g., Lalouni et al., 2017; Sankarpandi et al., 2017).

5. Participants

Patients will be offered i-CBT if the following criteria apply:

Inclusion criteria:

1) Age ≥ 18.
2) A primary diagnosis of functional disorders, gastrointestinal, specifically irritable bowel syndrome operationalized by ROME IV (DR58)

3) Normal recommended routine medical investigations: growth, blood samples including TSH, total IgA, IgA-tissue transglutaminase, complete blood count, erythrocyte sedimentation rate and C-reactive protein analysis, liver enzymes and fecal calprotectin.
4) Refractory gastrointestinal functional symptoms despite medical treatment (in accordance with guidelines)
5) Stable dosage of FGID-related medication such as laxatives, Imodium or pain-modulating psychopharmacological medication during the past month.
6) Living in Denmark.
7) Access to a computer or tablet with an internet connection.

Exclusion criteria:

1) Another disease that explains the symptoms.
2) Chronic inflammatory bowel disease (e.g., Crohns, colitis ulcerosa).
3) Lactose intolerance, celiac disease, and food allergies, in accordance with guidelines.
4) Severe psychiatric problems (e.g., suicidal ideation, depression).
5) Insufficient language or computer skills.
6) Addiction to alcohol, drugs or medicine.
7) Treatment with opioids or other addictive drugs such as benzodiazepines
8) Lactose-/gluten-intolerance where the diet has *not* been adjusted accordingly.
9) Severe cognitive or intellectual dysfunction or diagnosed autism spectrum disorder, which prevent the participant from interaction with the program
10) Ongoing psychological treatment.

6. Adverse effects, risks and drawbacks

No severe negative effects are expected from the treatment or the study procedures. This has been confirmed from the evaluation of the Swedish treatment programs (Ljótsson et al., 2010, 2011, 2014). Further, few drawbacks are expected, and may count the time patients' needs to spend on filling in questionnaires as well as time spent in the treatment program

7. Biological material

Not applicable

8. Information from patient records

- Patients are informed that their informed consent gives access to the following: **a.** Information from the Electronic Patient Journal (EPJ) and includes:
- gender, age, ethnicity,
- Diagnoses and examinations
- Use of medication, tobacco, alcohol, narcotics
- Information on social and psychological factors

b. The informed consent allow the research leader or any other control authority or instance to access the Electronic Patient Journal (EPJ) directly to access information on the participants' health status in order to secure good clinical practice during the treatment period.

9. Handling of person information in the study

Data will be handled according to Danish law on the Data Protection Act and the Data Protection Regulation.

All personal data including name, telephone number and social security number is encrypted.

The platform hosting the treatment programs has been developed and programmed at Functional Disorders, Aarhus University Hospital. The platform (internetbehandling.dk) utilizes the Drupal Content Management System (CMS) as a framework. That is, the user creation, login procedure, storing of data in database fields and so on are controlled by the standard modules and components built into the CMS. The custom functionality is written as Drupal plugins in object-oriented PHP making it easy to flexibly update and replace parts of the system when necessary. All access to the server goes through an encrypted SSL-connection, and data pooling is being logged with IP and user-ID. NemID/MitID is used to log in to the platform.

Access to the questionnaire data is only granted to researchers in the project and the data will be kept anonymous after project-end.

10. Transfer of personal data/biological material abroad

Not applicable

11. Economy and project organisation

A. Organization

The Danish FGID Treatment Study is a joint cooperation between Regional Hospital Silkeborg, Department of Functional Disorders (FL), Aarhus University Hospital, the Research Unit at the Department of Child and Adolescent Psychiatry (BUA), Aarhus University Hospital, the Department of Clinical Medicine (CM), Aarhus University, and the Department of Clinical Neuroscience (CNS) at the Karolinska Institute in Stockholm, Sweden. The study is organized by a research project team, a steering group, and international expert advisors, which will ensure availability of relevant expertise.

Research project team: Lisbeth Frostholm (Principal Investigator; FL); Charlotte Ulrikka Rask (Principal Investigator; BUA); Karen Hansen Kallesøe (BUA); Heidi Frølund Pedersen, (FL); Lotte Fynne (RHS); Lise Gormsen (FL); Laura Krogsgaard (FL).

Steering group: Lisbeth Frostholm (FL); Charlotte Ulrikka Rask (BUA);

International expert advisors: Brjánn Ljótsson (CNS); Erik Hedman (CNS)

Professor Lisbeth Frostholm, Functional Disorders, Aarhus University Hospital, and clinical professor, Charlotte Ulrikka Rask, the Research Unit at the Department of Child and Adolescent Psychiatry, Aarhus University Hospital, have initiated the present project in collaboration with the Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden.

B. Funding

The project is funded by:

- Tryg Fonden with 3.050.256 DKK

C. How the funding is used

The funding covers translation of the treatment programs, salaries, and webdevelopment

D. Administration of economy

The funding for this project is administered by Functional Disorders, Aarhus University Hospital, and the researchers have no affiliation to the funds.

E. Affiliations and conflict of interests

The funders of the study have no role in the study design, data collection, data analysis, data interpretation, or writing of manuscripts. Further, the involved researchers have no conflict of interest regarding economy or affiliation to the funds.

12. Remuneration

No remuneration is offered for participation in this study

13. Recruitment

a. Identification: The participants are recruited from the gastrointestinal department at Regional Hospital Silkeborg (RHS). Eligible patients are informed about the project by the medical doctor (oral and written information).

b. Informed consent

i. All participants receive written and verbal information about the project at the initial conversation with the recruiting medical doctor

ii. The conversation in which the information is given, is conducted by the medical doctor at her office ensuring a confidential setting

iii. Patients are informed that they have a right to bring a support person. If they did not bring a support person and wishes to do so, a new appointment will be scheduled, which can either be performed as a video consultation or in person .

iv. Patients have the right to consider participation for a week. If a patient wish time for consideration, s/he will be invited for another video consultation one week later, in which written consent is obtained via REDCAP. If this is not needed, written consent will be obtained at the first consultationeither in writing on paperm which will be digitalized afterwards, or via REDCAP using MitID as identification. When signing the consent form the participants give permission to publish the research data including clinically obtained information from the assessment, and give permission to be contacted if they are absent from the treatment or if they have not filled in the questionnaires.

There will be a clear declaration from the project research team that the individual patient can decline to participate in the study and the treatment at any time. This will not affect the patients' regular health care contact or treatment as the study is conducted outside of those settings.

c. First contact after informed consent: After the informed consent is given, patients are invited to a brief clinical psychiatric screening performed by a psychologist with specialty in functional disorders. A consultant in psychiatry will be available for supervision. The main aim of the screening is to evaluate in- and exclusion criteria including screen for psychiatric disorders, which will be done with a short version of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; WHO, 1998). If patients are not eligible for participation, they will be excluded from the project, otherwise they will be given access to the treatment program.

14. Publication of results

Positive, negative and inconclusive results will be made public via www.clinicaltrials.gov as well as published in international peer-reviewed journals.

15. Ethical considerations

The project is conducted in accordance with the rules in the Helsinki-Declaration. The project will beregistered under the Central Denmark Region's records of research projects (Den interne fortegnelse over forskningsprojekter ved Region Midt,) and it will be reported to the international database for clinical trials (clinicaltrials.gov).

No adverse events or side effects are expected. However, data on possible negative effects of the treatment will be obtained. The internet-based format will make this treatment available for patients who live far from specialized clinics and who are interested in a format that interferes less with daily life. A disadvantage of the treatment is that the participants will be expected to use approximately 4 hours per week.

Currently there is no systematic evidence-based treatment offers available for patients with FGID, despite the large negative impact the disorders have on patients' lives. The treatment programs have been previously tested and found efficacious in Sweden, and participants are therefore expected to benefit from participating by experiencing reduced symptoms and increased quality of life.

All participants are offered the active treatment program, and it is therefore a positive opportunity for each included participant. The current project can potentially help solve the unmet treatment need for Danish patients with FGID and pave the way for dissemination of evidence-based treatment. This can especially be the case for the large group of patients with a moderate degree of FGID who are primarily seen in the gastrointestinal departments where accessibility to cost-effective treatment is very scarce.

Thus, this study can help qualify the effect and feasibility of specialized psychological treatment for a patient group where few effective treatment options currently exist, thus ensuring that more patient's will have access to specialized and effective treatment for FGID in the future.

16. Compensation

The study is included by the rule on patients right to compensation ("Lov om klage og erstatningsadgang"), when participating in a scientific research project and patients will be informed about this at the initial assessment.

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