Research plan

Taking the LEAP: A randomized, naturalistic effect evaluation of the compuLsive Exercise Activity Program (LEAP) - a cognitive behavioural program specifically targeting compulsive exercise in patients with eating disorders..

BACKGROUND

Within the mental health field, physical exercise is valued as an effective means of alleviating depressive symptoms, and the anxiolytic effects of exercise have been well documented (Callaghan, 2004). However, when exercise becomes rigid and forced, coupled with an inability to stop despite negative consequences (e.g. injuries), then exercise is considered *compulsive* and may cause both physical and psychological harm (Meyer, Taranis, Goodwin & Haycraft, 2011). The goal of compulsive exercise (CE) is to control weight and body shape, to compensate for food intake, and/or to regulate or avoid negative emotions (Meyer, et al., 2011). CE is a common and prominent symptom in various presentations of eating disorders (EDs). EDs are severe and often long-term psychiatric illnesses, featuring high rates of both medical and psychiatric comorbidity and a pronounced risk of death (Berkman, Lohr & Bulik, 2007). A significant proportion of patients (between 25-50% depending on ED diagnosis) are still ill 10 years following treatment intake (Keel & Brown, 2010). Lifetime prevalence (age range 15-60) of EDs in Sweden today is about 3.5% (Clinton & Birgegård, 2017). CE is recognized as an important factor in ED etiology, development and maintenance (Kostrzewa, Eijkemans & Kas, 2013; Meyer, et al., 2011). In a nationwide study of adult Swedish ED patients, CE was reported by about half of all patients (Monell, Levallius, Forsén Mantilla & Birgegård, 2018). Previous studies have found prevalence of CE to be highest among anorexia nervosa (AN) patients (Dalle Grave, Calugi & Marchesini, 2008), but in our sample patients with bulimia nervosa (BN) and patients with other specified feeding and eating disorders (OSFEDs) reported the highest prevalence of CE. More importantly however, CE was clearly prevalent in all ED diagnoses and almost as common among males as among females. Of note, a 2011 nationwide study on Swedish ED patients (Welch, Birgegård, Parling & Ghaderi, 2011) found lower overall CE rates, but higher rates of binge-eating and purging, than we did. This suggests CE is becoming more prevalent as a symptom, and/or that there might be gradual symptom-shifting among ED patients over the years, with CE possibly coming to replace other ED behaviors. This pattern is also indicated in the latest annual report from the national Quality Register Riksät (Birgegård, Norring & Norring, 2016).

In adult ED patients, CE is related to more severe pathology (particularly dietary restraint and self-criticism), longer lengths of hospitalization, increased risk of relapse, and a more chronic course in AN (Carter, Blackmore, Sutandar-Pinnock & Woodside, 2004; Monell, et al., 2018; Solenberger, 2001; Strober, Freeman & Morrell, 1997). In addition, ED patients who continue or start with CE during treatment, have significantly lower remission rates at 1-year follow-up compared to patients without CE and patients who cease with CE during treatment (Levallius, Collin & Birgegård, 2017; Monell, et al., 2018). To date, there is no "gold standard" treatment developed to tackle CE. However, our and others' results indicate a clear need to address CE in ED treatment in order to potentially improve prognosis for a large proportion of patients.

There are promising preliminary findings for an empirically based targeted cognitive-behavioral intervention: the CompuLsive Exercise Activity TheraPy (LEAP; Taranis, Touyz, La Puma & Meyer, 2011). LEAP is founded on the same theoretical principals as the evidence based ED treatment: Cognitive Behavioral Therapy Enhanced (CBT-E, Fairburn, 2008) and may be offered as a complement to CBT-E. The aim of LEAP is not to make

patients stop exercising, but rather to promote non-excessive "healthy" and functional attitudes, beliefs and behaviors in relation to physical activity. LEAP is delivered in groups and consists of 8 one-hour sessions, stretching over 4 consecutive weeks. LEAP has been evaluated in two pilot studies and one RCT. In these studies focusing adult AN patients, LEAP reduced pathological exercise, ED psychopathology, general psychopathology, and length of hospitalisation; it also improved attitudes and beliefs toward exercise, BMI, and quality of life (Hay, Touyz , Arcelus, Pike, Attia, Crosby, 2018; Meyer & Touyz, 2011; Touyz, Meyer & Taranis, 2010). These promising findings need to be confirmed at other sites and with other ED diagnostic groups. Of note, the patients in the RCT had suffered from AN (known as an illness notoriously difficult to treat) for an average of 9 years- a considerably long time, yet they made important progress. The effects of LEAP with other ED diagnostic groups and patients with shorter illness duration may therefore be even greater. To our knowledge, there is no specialized ED treatment unit in Sweden today that offers interventions specifically designed to target CE. Judging by preliminary findings, the LEAP program may fill this gap, although more research on its efficacy in different ED groups is needed.

AIM

The project aims to evaluate the efficacy of LEAP at reducing pathological exercise and improving ED pathology in Swedish patients diagnosed with AN, BN, or OSFED, in a naturalistic randomized controlled trial (RCT). The project is a collaboration with specialist ED clinics (Eriksbergsgården, Örebro; Ätstörningsenheten, Göteborg; and collaboration with several additional clinics is possible too). Based on pilot data and power analysis, a total of 128 eligible adult patients will be recruited via the clinics and randomised to treatment as usual (TAU) plus LEAP (intervention group), or TAU only (control group). We will measure key outcome variables in both arms at initial assessment, after 3 months and 6 months after initial assessment. **Primary outcomes**: remission of ED diagnosis, improved ED cognitions, and reduced pathological exercise behaviours and cognitions. **Secondary outcomes**: normalised weight (BMI) and reduced general psychopathology.

RESEARCH QUESTIONS

*Primary research question: what are the treatment effects of LEAP on ED diagnosis, ED cognitions, CE behaviours and cognitions, BMI, emotion regulation and general psychopathology, after 3 months and after 6 months?
*Secondary research question: are there initial factors (e.g. BMI, emotion regulation, compulsivity) that predict a more favourable outcome for patients in the LEAP group?

STUDY DESIGN, METHODS AND MATERIAL

Study design. Two-armed parallel open-label superiority randomized efficacy trial, with recruitment from several specialist ED clinics and randomisation to TAU or TAU+LEAP, where LEAP will run in parallel with TAU. Data collection at baseline (T1), after 3 months (T2) and 6 months after initial assessment (T3).

Randomisation, masking and control. Each eligible patient consenting to participate will be assigned experimental condition by an allocating investigator (AI), using an online random number generator, stratified by site, diagnosis, and gender. The AI is the only person with access to randomisation group data. Clinicians conducting pre- and post-assessments are blinded, and LEAP clinicians do not carry out assessments. Participants cannot be blind to group, since LEAP deviates too much from standard ED treatment. The principal investigator (PI) will be blind to group until data have been analysed. All LEAP sessions

will be audiotaped, possibly videotaped. Two random sessions from each LEAP group will be externally assessed in order to monitor adherence and fidelity. Also, participants will answer questions about the content of their treatment at T3 including how much attention has been given to pathological exercise and in which ways.

Participants. Male and female patients, ≥18 years, with AN, BN or OSFED (Atypical AN and BN/Binge Eating Disorder with low frequency and/or limited duration of symptoms), reporting CE at T1 (EDEQ item 27, see *Instruments*), and entering outpatient care at a specialised ED treatment unit. Exclusion: previous specialised ED treatment, inability to communicate in Swedish, psychotic disorder, high suicide risk, and/or BMI<14. As more females than males seek treatment, there will be more females than males in the final sample. We aim for 98 participants (49 in each arm) completing the trial. With an estimated drop-out rate of 25%, we will enrol 128 participants (66/arm). A conservative estimate for inclusion is 18 months. As there is a minimum of 6 participants in a LEAP group, length of time between initial assessment and first session of LEAP will vary for patients. This variation will need to be considered a covariate.

The intervention. Standard outpatient care offered to both groups includes a medical contact, psycho-education about EDs generally, in the majority of cases a CBT-based treatment via a personal therapeutic contact and/or group therapy, and meal-support. Each individual has a personalised treatment plan. There are no systematic interventions focusing on pathological exercise in TAU, which means that TAU+LEAP will clearly deviate. LEAP, which is an addition to TAU running in parallel, is a semi-structured, problem-oriented CBT, with psycho-education specifically focusing on physical activity, behavioural experiments, and cognitive activities. LEAP is founded on the same theoretical principals as the evidence based ED treatment: Cognitive Behavioral Therapy Enhanced (CBT-E, Fairburn, 2008) and may be offered as a complement to CBT-E. The overarching aim is to promote "healthy" exercise. Specific aims are to: educate patients about the maintenance of CE; promote insight into factors affecting beliefs and behaviours toward exercise; introduce skills to help challenge maladaptive beliefs and behaviours; introduce adaptive emotion coping strategies; and prevent relapse. Each group contains 6-8 participants. The programme consists of 8 one-hour sessions over four consecutive weeks. Sessions are preceded by homework tasks. Groups will be held at the treatment units. Two therapists at each treatment unit and three additional therapists from the research group (two acting as supervisors) will be trained in LEAP by Prof. Caroline Meyer and Prof. Jon Arcelus.

The control group. These patients receive standard outpatient care (TAU), personalised to suit their individual needs. Pathological exercise will not receive systematic attention since this is not standard practice. However, the attention given to exercise as a symptom may vary between therapists. Thus, to control for potential deviations from standard practice in this regard, participants will answer questions about treatment content at T3.

Instruments.

1. Structured Eating Disorder Interview (SEDI, diagnostic interview)
2. The Compulsive Exercise Test (CET) measuring aspects of CE (e.g. rigidity and weight control exercise; LEAP group only).
3. The Eating Disorder Examination Questionnaire (EDEQ), using gender-specific scales, to measure e.g. ED cognitions, restraint and presence and occurrence of CE.
4. BMI

5. The Difficulties in Emotion Regulation Scale (DERS) measuring problems with emotion regulation.
6. The DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure (general psychopathology)
7. Treatment content questionnaire measuring content of treatment retrospectively

Procedure. Patients come to the clinic via clinical or self-referral. Within the first three visits, they are assessed using standardised diagnostic interviews, clinical rating scales, and self-report questionnaires (e.g. CET, EDEQ, DERS). Clinicians record height and weight. Patients who meet inclusion criteria will be informed about the study; those who are interested will be contacted by the AI, who will provide further information and collect written informed consent. The AI will then conduct randomisation and inform participants and LEAP therapists of the result. Data at baseline (T1) is collected via Riksät (the national Quality Register) and Stepwise (a clinical support system for specialist ED care). All instruments above except the CET, are included in Riksät/Stepwise. CET will be collected separately by a research assistant in the project group via BASS Core Facility (a secure and encrypted tool for collecting questionnaire data online). Data at T2 (3 months after initial assessment) instruments 2-6 above, and data at T3 (6 months after initial assessment) instrument 1-7 above, and 6 (instrument 1-7) months follow-up (T2 and T3) will be collected by the research assistant via BASS Core Facility. Participants who complete the follow-up questionnaires are rewarded a 100 SEK gift card (Superpresentkortet)/follow-up occasion.

Statistical analysis. For differences between TAU and TAU+LEAP, a two-way repeated ANOVA will be conducted for each continuous primary and secondary outcome measure (i.e. group*time), with gender, baseline of each outcome, and time between T1 and first treatment session as covariates. For the dichotomous outcome variable of ED diagnosis, a repeated measures Chi^2-test (2 groups with binary outcome), the McNemar test, will be applied. Statistical power with beta=.80, alpha=.05, effect size f=.25 and an estimated correlation between pre- and post-measures of .50, requires a total of 98 patients; 49 patients receiving LEAP and 49 controls. Multiple regression will be used to investigate prognostic factors in response to our secondary research question. To analyse dropout and loss to follow-up within the groups, conventional tests (t-test, chi^2) will be used.

WORK PLAN

Fall 2019: Contact with specialist ED clinics where evaluating LEAP is possible, has already been initiated, and in preparation for this project year we will continue to foster those contacts, aiming to establish a close collaboration with key figures within the organizations. All the details around the evaluation (for instance, how and when clinicians inform eligible participants about the study, details around the follow-up procedure) and its structure will be discussed in collaboration with the clinics. Practical concerns, such as for example when and where the LEAP sessions should be held (e.g. at the clinic or elsewhere) will also be dealt with collaboratively. In parallel, establishing good communication with the researchers at the Loughborough University and the Warwick University (Prof. Caroline Meyer primarily) and the researchers who carried out the RCT on LEAP in Australia (Prof. Phillipa Hay primarily) will be of high priority. Their experiences of working with and evaluating the LEAP will be carefully considered when further designing our evaluation of the program.

Spring 2020: Prof. Meyer and Prof. Arcelus are scheduled to come to Stockholm and hold a clinical workshop/clinical training in how to deliver LEAP April 2020. Data collection and recruitment of participants will begin fall 2020.

Fall 2021-Winter 2022: Throughout this time period, the focus will be on collecting data and running the LEAP groups. At least two groups can run in parallel and as the time frame for each group is four weeks, we have the potential of running about 16 groups in total during this time period. However, depending on the randomization and on how slow the inclusion is, a conservative time estimate for inclusion is 18 months. 10 groups will be sufficient to reach our goal of 49 participants in each arm (also accounting for a high estimate of 30 % drop-out).

Spring 2023: During the early spring we will begin analyzing pre- and post-data for each group. The focus during this period will then be to write up the results and communicate them to the clinic, others with an interest in the project (e.g. Prof. Meyer and Prof. Hay), in international journals, in more public settings and at international conferences within the ED field. Around May the follow-up data collection should be completed and thus analysis and the writing-up of those data can commence.

CLINICAL SIGNIFICANCE

The project has clear clinical utility since it is aimed at enhancing TAU by targeting the most common behavioural symptom in patients today, and about 50% of ED patients may benefit, with remission and recovery hopefully improving as a result (suggested by previous studies). EDs are often long-term and may require periods of hospitalisation. Preliminary results suggest LEAP reduces the length of hospitalization and as it reduces CE, may also improve the chances for recovery. Improving recovery rates is of course beneficial for patients, but also for society (in terms of reducing costs of long-term treatments and hospitalizations).

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