Bilaga 2

Lifespan integration after sexual trauma

A randomized controlled open treatment study with a blinded evaluator at the Wonsa clinic for individuals suffering from sexual trauma or abuse – is Lifespan Integration a suitable treatment method after sexual trauma?

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We hereby certify that researchers conducting the present project promise by their signature to as far as possible due to the character of the study follow (not being a clinical trial evaluating a pharmaceutical drug) ICH and GCP.

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Summary

The planned study is a randomized controlled trial with intention to treat (ITT) analysis, where people 15 years of age and older who have been involved in a single sexual trauma during the last five years are randomized to either a new trauma treatment method, Lifespan Integration (1), or to a waiting list. After 2 weeks, participants on the waiting list are also offered Modified Lifespan Integration. We intend to measure the effect on post traumatic stress (PTSD) symptoms three weeks after the intervention, and 6 months after the intervention. We plan to conduct the study in collaboration with the non-profit organization World of No Sexual Abuse (WONSA).

Lifespan Integration is based on the assumption that the traumatic event that needs to be treated has not been integrated into the course of life and that the patient without integration is unable to fully realize that the event has ended. This is believed to be the cause of the symptoms seen in posttraumatic stress and PTSD. By following for a period of 90 minutes a repetitive protocol and an individual timeline ranging from the specific trauma to the present, the specific trauma is addressed. The method is relatively new, but two studies on Lifespan Integration have been conducted: a case study 2013-2014 (Trinity Western University Lifespan Integration Efficacy Research Study, Vancouver, Canada) (2) and a 2012 cohort study (Lifespan Integration Effectiveness in Traumatized Women, Seattle, USA) (3). The results of these studies have been promising. For more information on Lifespan Integration, see the manual.

The Agency for Health Technology Assessment and Assessment of Social Services in Sweden, recommends the psychological treatment methods Cognitive Behavioral Therapy (KBT) and Eye Movement Desensitization and Reprocessing (EMDR) for patients with PTSD. Both methods are based on exposure to the trauma and have been given evidence level 2. At the same time, it is noted that the methods have a lower effect in interpersonal trauma than in other trauma, and that the patient rarely becomes completely asymptomatic and that symptoms often recur after completion of treatment (4). Another method of treatment with a different theoretical background and described mechanism of action could provide new knowledge about the mechanisms behind PTSD and also provide immediate patient benefit.

Background

6000 rapes were reported in Sweden in 2013, and approximately 600 women sought care at the emergency department for raped women at Södersjukhuset in Stockholm (5, 6). Rape is the trauma that, together with the threat of war, is the leading cause of incident PTSD diagnoses in epidemiological studies (7). PTSD is a condition that occurs when a person who has been involved in a scary event resuscitates and continues to be strongly affected psychically and / or somatically by the incident four weeks after the event occurred. The symptoms included in the diagnosis are specified in DSM 4. and include four main criteria where reverberation (nightmares, intrusive memories, physiological reactions, flashbacks, etc.), avoidance of things that remind you of the event, and indifference are included. In a newly published study of 201 participants from the emergency department for raped women at Södersjukhuset in Stockholm, 34% of the participants had remaining symptoms of PTSD 6 months after the emergency visit (8).

Today, the most common treatment of PTSD are based on exposure. Exposure can be made of both thoughts, feelings, things and places that are linked to and / or remind of the event. Prolonged Exposure has one of the methods with beneficial evidence in randomized controlled treatment (9). The treatment protocol is based on 9-12 treatments each 60 minutes long, and daily work with different types of exposure as "homework" between treatments. For example, a normal homework may be to record a detailed description of the traumatic event, and then listen to this recording every day. A more cumbersome treatment method that requires fewer sessions would be of value to the patient group.

In the planned study, the efficacy of Lifespan Integration, is evaluated. We have chosen to study the method because:
A) it offers an alternative to traditional exposure (1)
B) The theory is in line with neurobiological research on neural networks and on neural plasticity. (10, 11)
C) The method is manual based, and for PTSD treatment only one session is used.

Lifespan Integration was developed by Peggy Pace (USA 2002) (1). Today approximately 2000 therapists are using the method. There are no prior studies published, but the anecdotal reports from therapists and patients using the method, is that symptoms of PTSD diminish already after one session. One unpublished outcome study was conducted by Balkus´ (2014). In this study 17 women at a women residential treatment program in Seattle, with different types of interpersonal traumas, worked with one chosen index trauma for two sessions of LI. Changes in Impact of Event Scale (IES) were used as primary outcome. There was a major score-reduction post treatment, and further score reduction was seen three months later (3).

Overall purpose

The overall aim is to investigate the hypothesis that Lifespan relieves stress symptoms after one treatment session, in individuals with stress symptoms and / or PTSD after sexual trauma. In the study, the original PTSD protocol by Peggy Pace is developed into a three phased manual, called Modified Lifespan Integration PTSD-protocol (MLI).

Hypothesis

Our hypothesis is that stress symptoms and symptoms of PTSD in women exposed to sexual trauma six months to five years earlier decrease significantly, in comparison with untreated control groups after treatment with one session of MLI.

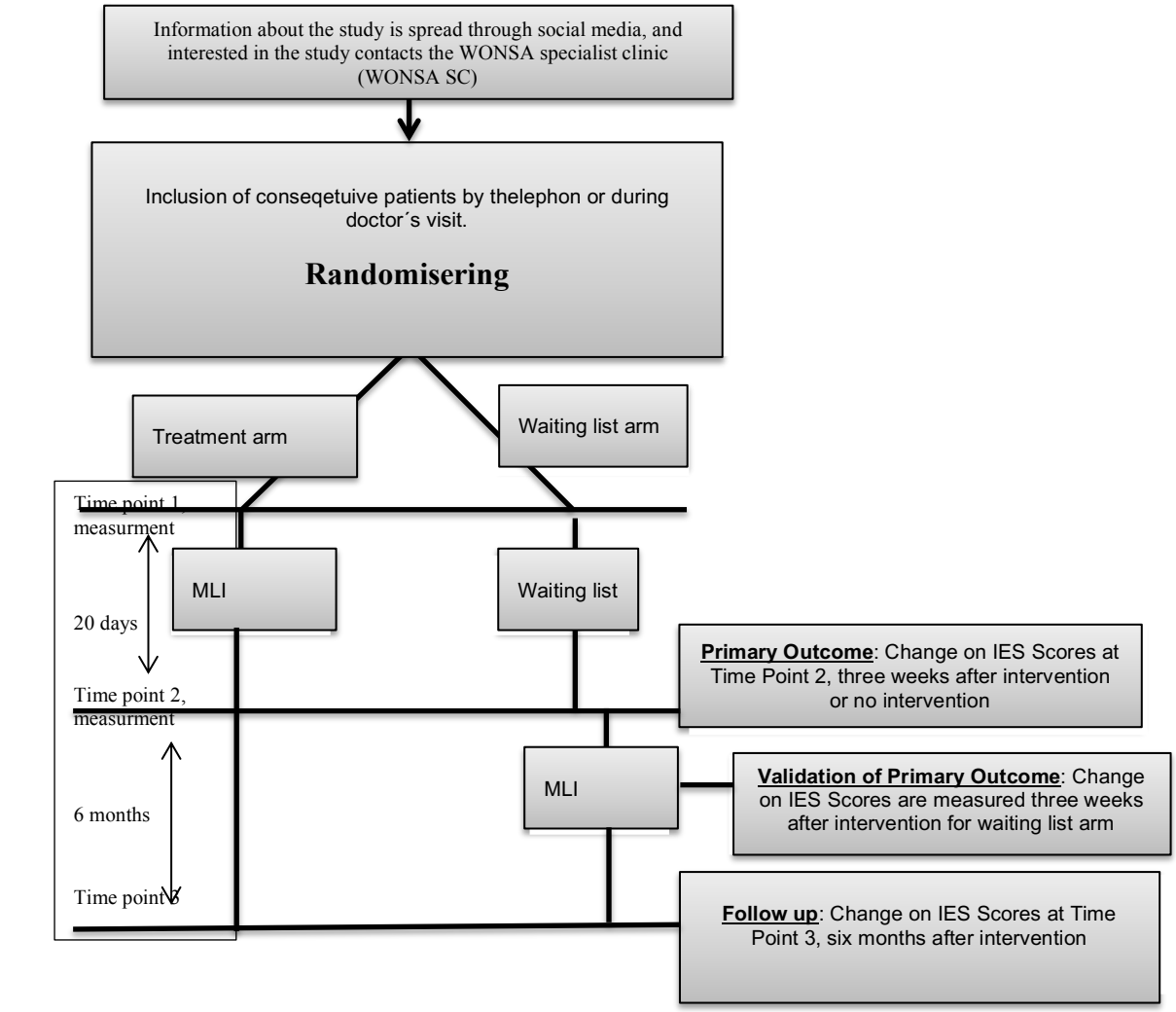
Specific aims

1. Does a 90-minute ±30 minute treatment session of Lifespan Integration have a significant effect on stress symptoms and / or PTSD after sexual trauma? Primary outcomes are the difference in change in the Impact of Event Scale estimates and self-assessed health from baseline (measurement 1), to measurement 2 (see Figure 1) between the group that receives Lifespan Integration and the group on the waiting list. Secondary measurements are the change of Stressful Events Survey PTSD Short Scale [NSESS] Form and Change of Medication Needs from Baseline 1 to Measure 2. All forms are listed in Appendix 5. Comparisons are made with the Control Group on the waiting list.

2. How does the effect look six months after treatment with MLI? Primary effect measurements are a change in the Impact of Event Scale estimates and self-assessed health

from measurement 2 to measurement 3 (see Figure 1). Secondary measurements are the change of Stressful Events Survey PTSD Short Scale [NSESS] Forms, Medication Needs and Illnesses from Measurement 2 to Measurement 3 (See Figure 1). Only patients who have been added to Lifespan Integration participate in this measurement. No control group is used in this analysis. All forms are listed in Appendix 5.

Bild 1.



Method and Design

The study is a randomized controlled non-blinded treatment study. In our study we will include 100 participants (see power calculation below). Randomization with fewer than 300 participants is not optimal from a statistical distribution perspective. However, we have chosen to randomize patients because it is a well-established method of getting as comparable groups as possible with as little bias as possible, despite a relatively low study rate.

Treatment studies can be done double-blind, single-blind or open (non-binded). Because it is a psychological treatment study, we can unfortunately not make the study blinded, but the

researchers who process the material will not know if the forms (self-assessments) have been filled by participants who have received the treatment or not.

Because the treatment consists of a single session treatment, it is not possible to use a cross-over design. We have therefore chosen to use a separate control group. We have chosen to let our control group be on the waiting list, as we want to check significant effect in relation to the placebo / waiting list.

Participants will for ethical reasons be on the waiting list for the shortest possible time (max 20 days +/- 3 days).

The primary outcomes are a difference in change in the Impact of Event Scale estimates and self-assessed health at the second measurement, among those treated with MLI and the Control Group on the waiting list for MLI.

Study population

The study population consists of individuals 15 years of age and older who have been subjected to self-reported rape or equivalent sexual trauma at one occasion, have a good understanding of Swedish and who do not have an ongoing abuse or mental illness. We will advertise for participants in traditional media and in social media (see ad in Appendix 3). The advertisement will be distributed in social media through WONSAS´ network where organizations (The association *HOPP Stockholm, Föreningen tillsammans, Föreningen Storasyster*) knows about the planned study and will help spread the ad in social media and to other non-profit organizations. Individuals interested in participating based on the advertisement are asked to contact WONSA, who set up the person for a visit where written and oral information about the study is given, and where inclusion of eligible people takes place.

Inclusion criteria are:

a) Individuals who are 15 years old or more at the start of the study, who has been exposed to one sexual trauma no later than 5 years before the start of the study.

b) Good understanding of Swedish.

c) Want to participate in the study.

Exclusion criteria are:

a) Ongoing psychosis.

b) Ongoing active abuse

c) ADHD, Autism.

People who want to participate in the study contact WONSA SC and are consecutively booked for telephone interview by a doctor. Consecutive elective patients are then asked for participation in the study until 100 participants are included in the study. Elective patients are patients who meet the inclusion criteria and lack the exclusion criteria. Before inclusion, eligible participants receive oral information. Written information and consent is sent via an

e-mail with a link to the participant, and written consent is given via the link before the assessment is sent to the participant. (Appendix 4). For safety reasons all participants meet the doctor before treatment. The information in Appendix 4 provided for the study to the researcher contains brief information on the background and purpose of the study, that the participation is voluntary and that the researcher can at any time cancel the participation without explanation and that all tasks will be processed and presented without the participant being identified. Information is also given about who is responsible for the study and where to turn for more information. Information is also given on the provisions of the Personal Information Act (PUL) according to the link "vägledning till forskningspersonsinformation" at www.epn.se. The number of participants is based on power calculation further down.

Those who choose to participate are randomized in the next step to intervention or to waiting list by envelopes taken from the orderly envelope box. Sequenced data-generated randomization and ordering of envelopes in envelope boxes are carried out by Karolinska Trial Alliance. The participant then receives time for treatment. For participants admitted to treatment, treatment will take place 5 days (+/- 3 days) after self-assessment 1. For participants who have been added to the waiting list, treatment takes place 5 days (+/- 3 days) after self-assessment 2. All treatments are done at Wonsa's clinic. Sound recordings take place in all treatments, in order to monitor compliance with the treatment protocol and compliance with good clinical practice.

A link via email, which leads to a self-assessment form (Appendix 5), is sent to the participant and must be completed by the participant 5 days (+/- 3 days) before the treatment. A link for self-assessment 2 is sent within 20 days (+/- 3 days). Participants from the waiting list will receive a link for validation of the treatment group results within 20 days (+/- 3 days) after self-assessment 2. A link for estimation 3 is sent to participants 6 months (+/- 6 weeks) after treatment with Lifespan Integration (q3). Reminder will be sent electronically and by mail two weeks after the first dispatch (+/- 2 days). After another week (+/- 2 days) we will call and remind participants who have not yet registered their data to fill in the self-assessment data.

Lifespan Integration is carried out by at least three different therapists to avoid confusing results by the individual personal qualities or qualities of different therapists. For more detailed description of the methods, see Appendix 12. All treatments are scheduled to be conducted at the WONSA SC. Audio recordings takes place in all treatments to ensure compliance with the treatment method, if necessary.

Participants who during the study for ongoing medical and / or psychological have to drop out of the study will be subjected to adequate treatment in collaboration with selected healthcare centers that may refer to other care units according to existing routines at the emergency department for raped women at Södersjukhuset in Stockholm. Participants who choose to cancel their participation in the study ("drop-out") will be invited to respond to the self-assessment 3. Participants who, after inclusion in the study, interrupt the participation, regardless of withdrawal, drop-out, , or other psychological or psycho-pharmacological treatment started, will be included in the "intentional-to-treat" (ITT) nature of the analysis, and self-assessment forms at the time of the discontinuation of the study will be analyzed as unchanged from the previous measurement. Separate per-protocol analysis will also be performed to calculate the effect of Lifespan Integration if you follow the protocol.

Study material and collection process

The study material consists of web-based surveys that are filled in before and after the intervention Lifespan Integration or waiting list. Data from all original paper surveys is entered into database by a research assistant.

Monitoring is done by an external reviewer from Karolinska Trial Alliance. The examiner continuously checks that the study is based on authentic patients, consent, primary variable, end-points, correct transfer from original documents to database, and study binder. The first review takes place when 3-5 participants are included. Based on the first monitoring, intervals for continued monitoring are decided.

All written documentation, will be filed and stored in locked space. Code number and the code key will be kept in a separate locked space and audio material in a further separate locked space. Studyguard with ethics and approval from the committee, consent, delegation list and screening list are kept separately and locked. Coding is not broken until all individuals' separate results are processed. The code key will be destroyed when all results are processed.

Researchers will have access to the written material continuously after monitoring. Lifespsan Integration is relatively new therapy method, but two studies on the method have been done: A case study was carried out 2013-2014 (Trinity Western University Lifespsan Integration Efficacy Reserach Study, Vancouver, Canada) and a Cohort Study Without Control Group 2012 (Lifespan Integration Effectiveness in Traumatized Women, Seattle, USA) . The results of these studies have been promising.

Power

In a first step, we want to show that Lifespan Integration is better than a placebo / waiting list for the treatment of stress symptoms and symptoms of PTSD. As a basis for the Power calculation, we have used Kazdin, A.E's power table for t-test (11). With significance level (alpha level) 5% and power (beta level) 80% and expected effect size 0.70, 33 participants required per treatment arm, ie 66 people in total. With a margin of 30% loss, at least 100 people should be included.

Ethical considerations

The participants have been subjected to a scary event. Participants have chosen to participate and are informed of the study and treatment method that will be used (Lifespan Integration). In the short term there is a risk that any interventions or actions that in some way reminds of the scary event creates an increased mental and physical discomfort. There is therefore a risk of increased discomfort for all patients on reception, regardless of participation in the study or not. Only one treatment is included in the study, and estimation forms allow for immediate deterioration. The treatment is done with experienced therapists who, during ongoing treatment, can capture unexpected reactions that may require another measure. There is preparedness to offer all participants who choose to cancel participation in the study or who experience impairment to be recruited for adequate treatment in collaboration with selected healthcare centers that can refer to other care units according to existing routines at the emergency department for raped women at Södersjukhuset in Stockholm. In view of the above, we consider that the possible gains consider the risks for the individual participants.

Schedule and dissemination

We planned to start the study during early spring of 2016. The police report nearly 1,000 rape on people over 15 years in Stockholm each year. With the help of advertising through Wonsa's network and nonprofit organizations for victims of sexual abuse, we estimated that it should take about 1 year to include all participants.

However, it has proved to be more difficult than we thought to include participants, and the original inclusion criteria have now been broadened, and webpages, telephone inclusion and travel allowance for participants outside of Greater Stockholm will make it easier for non-Greater London participants to participate.

Processing of materials will take place continuously. By the end of summer 2018, all material is expected to be submitted for the main outcome and six months later also for secondary outcomes. Final processing and final analysis are made 2017-2018. Articles are intended to be written and published in scientific journals.

Scientific and practical usefulness

Lifespan Integration has a different described mechanism of action than today's evidence-based methods for the treatment of stress symptoms and PTSD. If treatment based on another described mechanism of action has an effect, it may bring new knowledge and new hypotheses about the mechanisms behind PTSD. Practical benefit of effective treatment of PTSD with few treatment options may be of great use to the research people in the project, and to potential patients in the future.

Gender perspective

The absolute majority of individuals exposed to sexual trauma are women (6). Effective treatment, however, is equally important for men as for women, and there is nothing that speaks for the method to be gender dependent. Both men and women may therefore participate in the study.

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