Acceptance and Commitment Therapy with Enhanced Mindfulness for Chronic Pain

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1. Project title

Acceptance and commitment therapy with and without enhanced mindfulness training for chronic pain: A randomized controlled efficacy and mediator study

2. Introduction

During the last three decades numerous population-based surveys have presented surprisingly high prevalence figures of chronic pain, according to a recent systematic review (1). Our united Norwegian pain research group has estimated figures in Norway between 24 (2) and 29% (3) of chronic pain and a pooled prevalence of 31% worldwide (1). Chronic pain is estimated to affect 100 million adult Americans at any given time and carries direct and indirect costs of over 600 billion dollars annually in U.S. alone (4). In Sweden the costs are estimated to be 32 billion EUR per year (5). Despite this, and the fact that The Global Burden of Disease studies show that chronic pain conditions are the most important current and future causes of morbidity and disability across the world (6), little has so far been done. Treatment measures that have been initiated, like opioid treatment and repeated blocks, have not alleviated this significant health and societal problem. On the contrary, widespread use of opioids against chronic non-malignant pain has caused a fatal opioid epidemic in the US (7). Pharmacological pain management is still indicated for chronic nociceptive and neuropathic pain, but in most cases of chronic pain, no cause can be identified. In a major clinical examination study of chronic pain in the general population, our research group has confirmed that in more than fifty percent of the cases, musculoskeletal pain conditions dominate and no cause for the pain condition can be identified (8).

As non-pharmacological alternatives, psychosocial treatments have been recommended for chronic pain management (9). One such treatment is Acceptance and Commitment Therapy (ACT). ACT is based on Relational Frame Theory (RFT), a comprehensive theory about language and cognition (10). Treatment intends to help patients identify values ("what is truly meaningful to them") and to set goals and take action according to their values. In addition, patients are taught mindfulness skills to increase acceptance of pain, thoughts and feelings so that they have less impact on functioning and action, but addition of daily mindfulness training at home is not included (10). ACT is considered a "third generation" variant of cognitive behavior therapy and has research support in the treatment of several mental health problems (11). Among patients with chronic pain, several small clinical trials have shown that ACT is superior to controls in terms of increasing function and improving mental health, with small to medium effect sizes (12). However, further methodologically robust trials are required (13). The primary aim of this study is thus to examine in a large sample of patients from four multidisciplinary pain centers whether ACT for chronic pain is more effective than a patient education program, and whether adding daily mindfulness training will improve the outcome.

The question is, however, not only if it is effective, but "why, for whom, and under what circumstances?". Mediators and moderators of change are important to sort out. Identifying specific variables that mediate the effects of a treatment on patient outcome could facilitate refinement of theoretical models and the development of more effective treatments. Minimal research has so far been conducted with the aim to identify treatment effect moderators such as patient characteristics (phenotypes) that help us to match patients to appropriate and effective treatments. This is supposed to be one of the most important directions for future research in chronic pain (14-16). Secondary aims are thus to identify for whom the treatment works, for whom it is not effective, and to identify key mechanisms of change so that more effective variants of the treatment can be developed.

Current theories of chronic pain emphasize an important role for attentional processes (17). Attention is often subdivided into three independent networks : 1) alerting- which is readiness in preparation for an impending stimulus, including tonic effects that result from spending time on a task (vigilance) and phasic effects that are due to brain changes induced by warning signals or targets, 2) orienting- which is the selection of specific information from multiple sensory stimuli, and 3) executive attention- which is monitoring and resolution of conflict between activity in different neural areas (18). Alerting involves the brain`s noradrenaline system, which originates in the brain stem and mainly in the locus coeruleus. Orienting involves frontal and parietal areas, including the frontal visual fields and inferior and superior parietal lobe. Executive attention involves the anterior cingulate cortex, anterior insula and basal ganglia (19, 20). Several recent studies have shown that patients with chronic pain have an attentional bias towards painful stimuli and other negative information (21-23). Moreover, recent meta-analyses have shown that patients with chronic pain have reduced executive function including working memory deficits (24, 25). Recently it has also been demonstrated that attentional functioning predicts chronic pain (26).

Mindfulness is typically described as non-judgmental attention to experiences in the present moment (27). It includes two modes of action: First, it requires the regulation of attention in order to maintain focus on immediate experiences such as thoughts, emotions, body posture and sensations. Second, it requires the ability to approach one's own experience with openness and acceptance. Practicing mindfulness meditation may enhance attentional control, alter self-awareness and improve emotion regulation. A systematic review found that early phases of mindfulness training might be associated with improvements in executive attention and orienting, while later phases might be more associated with improved alerting (28).

Three studies have used neuroimaging to evaluate changes in pain processing through mindfulness training. Beginners showed increased activity in anterior cingulate cortex and anterior insula which are areas involved in the cognitive regulation of nociceptive processing, increased activity in the orbitofrontal cortex which is involved in reframing the evaluation of stimuli and reduced activity in the primary somatosensory cortex (29). Experienced users of mindfulness training showed decreased activity in dorsolateral and ventrolateral prefrontal cortex and increased activity in primary pain processing areas such as the insula, somatosensory cortex and thalamus (30, 31). These findings suggest that mindfulness training alters the brain differently over time and has significant influence on cognitive processing over time. Although it is documented that brain regions relevant for the regulation of attention and pain show functional and structural changes following mindfulness training, it is not known whether these changes are actually related to improvements in attentional functioning and clinical outcomes among patients with chronic pain. If it turns out to be so, one may have discovered a major mechanism of change in pain processing and symptom reduction. Thus, one main aim of the present study is to examine if mindfulness training improves attentional functioning and if this potential improvement enhances the amelioration of pain.

In ACT, mindfulness is included in ways to increase acceptance and psychological flexibility, but does not necessarily involve systematic practice over time(10). We will therefore investigate the effects of adding prolonged mindfulness training to ACT delivered to patients with chronic pain. Since mindfulness training may affect the brain differently over time, it is important to measure attentional functioning after early phases of mindfulness training (after four weeks) and after training systematically over a longer period (six and twelve months).

Although improvement of attentional functioning may be a central mechanism of change (group level), it may not be an important mechanism of change in all patients (individual level). Several mechanisms, biological, psychological and social, have been suggested to maintain chronic pain

(32). It is reasonable to assume that all these mechanisms are more or less important in different pain conditions, in patients with different psychological makeups and patients living under different social and occupational circumstances. Some have argued for applying personalized or individualized treatment (33). As stated by Jensen in a comprehensive review in Pain (9): "If a clinician limits himself or herself to only one of the existing theoretical models or psychosocial treatments, then a subset of that clinician`s patients will be unlikely to receive optimum care." We assume that it is vital to examine and diagnose each patient thoroughly in a standardized way before the start of a treatment trial to make it possible to identify common characteristics of patients who do not benefit much from the treatments (predictors of poor outcome). It also makes it possible to identify characteristics of patients who may profit more from one treatment than the other treatments (differential treatment effects). This is a second aim of the present study, namely to identify clinical predictors and moderators of change and possibly to identify distinct phenotypes.

The research project has several methodological strengths:
1. This will be the largest controlled study on ACT for chronic pain so far. Most patients with chronic pain without known cause referred to all the four major multidisciplinary pain centers in all health regions of Norway will be asked to participate in the study.
2. The patients will receive high quality evidence based assessments by clinical experts specifically trained in pain diagnosis and given treatment conducted by highly qualified therapists with adequate training. Improvement in the quality of clinical practice in all regions in a standardized way will be the result immediately from the start of the project.
3. This multisenter study will have coordinated data and equal treatment implementation since the four multidisciplinary pain centers already coincide with diagnosis, assessment and treatment. In the fall of 2017 they had a two-day meeting where all four presented their ACT group program for closer co-operation. Thus, the multicenter study is therefore highly feasible.
4. The four centers have a response rate on internet-based self-report on almost 100% pre-admission and about 80% one year after treatment from four identical online quality records. This self-report system will be used in the study and has been published as feasible by our research group (34).
5. It should be possible to identify patient characteristics (phenotypes) that can guide clinicians in the future in the selection of which of the patients are likely to profit from ACT, and which patients are likely to receive benefits from the addition of mindfulness training.
6. It should also be possible to identify patients who benefit less from the treatments and who may need other alternatives. Patient characteristics can help us to identify key target components in the development of new treatments for these patients.
7. The theoretical hypothesis aiming to identify a key mediator of change is based on modern cognitive neuroscience including thorough neurobiological studies of the human brain.
8. Both for self-report measures and attentional functioning the study will use safe computerized test systems the patients can complete in their homes. This will make it possible to increase the number of assessments without the subjects needing to return to the outpatient clinic. This will increase the quality of assessments and reduce the cost
9. Since the study includes self-report assessment methods that are easy to deliver and score, it is also easy to translate the knowledge and procedures to other treatment facilities in Norway and internationally after the project period.

2.1 Need description
Patients referred to tertiary multidisciplinary pain clinics are those who generally have very poor functioning and they have often tried many standard treatments without effect. Many have experienced unsatisfactory or adverse effects of medication. To establish the efficacy of a psychological therapy would be of major benefit for this group of patients living with refractory

chronic pain. This multi-professional study has the potential to strengthen the disciplines by increasing our knowledge about efficacy of an increasingly popular psychological treatment. If shown efficacious and feasible, this study should provide evidence for educating other therapists working with chronic pain patients in the method. Investigating key methods of change may give knowledge necessary for developing and improving the therapeutic method.

3. Hypotheses, aims and objectives

The primary aim of the study is to investigate the effectiveness of ACT (group 1) and whether adding a component of mindfulness training (group 2) will improve outcomes on pain (primary outcome), attentional functioning, physical functioning and mental health (secondary outcomes), compared to a control group (group 3). A secondary aim is to assess the degree to which improvement in attentional functioning can act as a mechanism of change (mediator) in pain. A third aim is to identify patient characteristics (phenotypes) that predict treatment effects (moderators of change), or, equally important, that predict failure to achieve benefit.

More specifically it is hypothesized that:
1. ACT is more effective in improving pain (primary outcome), mental health and physical function (secondary outcomes) at 52 weeks compared to the controls (paper 1).
2. ACT with an additional component of mindfulness training will be significantly more effective in reducing pain and improving mental health and physical functioning at 52 weeks than ACT without mindfulness training (paper 1).
3. Patients receiving ACT with mindfulness training will from treatment start to treatment termination show significant improvement in orienting and executive attention reflecting enhancement in top down processing compared to those receiving ACT without mindfulness training and compared to control (paper 2).
4. Patients receiving mindfulness training and continuing to practice until 32 weeks of follow-up will show significant improvement in alerting, reflecting enhancement in bottom up processing at 52 weeks follow-up compared to those who have discontinued practicing (paper 2).
5. Patient improvement in alerting and executive attention during treatment predicts a reduction in pain at eight and 16 weeks of follow up (paper 3).
6. Patients who continue to practice mindfulness training until 32 weeks of follow-up will report less pain at 52 weeks follow up compared to those who do not (paper 3).
7. Patients with initial higher levels of attentional functioning, will report a significantly higher reduction in pain and improvement in physical functioning and mental health (paper 4).
8. Patients with neuropathic pain, psychiatric and sleep disorders will have a worse outcome independent of treatment received (17) (paper 4).
9. The cost effectiveness of ACT for chronic pain is superior to patient education (paper 5).
10. Effects of ACT are maintained at three years follow up (paper 6).

4. Project methodology

4.1 Project arrangements, method selection and analyses

4.1. 1. Sample

At least 486 patients will be included in the study (see power analyses below). Patients will be included if they are referred to one of the pain clinics with a primary diagnosis of chronic pain lasting for at least six months. About 200 patients will be recruited from Oslo, 200 from Trondheim, 100 from Bergen, and 100 from Tromsø. Exclusion criteria will be severe somatic disease or severe mental disorder (ongoing mania, psychosis, suicidal ideation or substance abuse/addiction). In addition will patients who cannot communicate in Norwegian or who need 24-hour personal assistance be excluded. Each treatment center will randomize the patients into three different research programs (see below).

4.1.2. Study design
This is a three group randomized controlled trial with 162 patient in each group, six different measurement points, of which pre-treatment and 52 weeks after start of the treatment are the crucial points.

4.1.3 Background for the interventions
The choice of treatment conditions is based on the following reasons: 1. Mindfulness training has shown to be effective in both stress and pain reduction (35-37). 2. Mindfulness training has shown to alter brain functioning (differently in the short and long run). 3. Mindfulness training uses relevant techniques for improving attentional functioning, both focused attention (top down processing) and open monitoring of present moment experiencing (bottom up processing). 4. ACT has been shown to be effective in improving mental health and physical function in patients with chronic pain, but less so in reducing pain (12, 13). 5. ACT uses mindfulness techniques that do not involve meditation or training, but this may be included in the treatment. The research design thus makes use of a component analysis which is under- utilized in pain treatment research (9, 38). It makes it possible to identify if patients who receive both components (mindfulness training and ACT) obtain more gains than patients who receive only one component. 6. The education program does not involve the same components of change (attentional functioning, learning to live according to ones values and acceptance) as mindfulness and ACT.

4.1.4 The intervention groups
ACT (group 1) will follow a manual based on the work of Steven Hayes and colleagues (10). The manual is adapted to a group therapy setting and includes all the dynamic processes of ACT; committed action, values, self as context, presence in the moment, defusion and acceptance It has previously been piloted and applied to a work rehabilitation setting by our research group (39). Two qualified therapists will lead every treatment session.
ACT with enhanced mindfulness training (group 2): ACT will be performed exactly as group 1, but in addition mindfulness exercises will be introduced in the ACT sessions and patients will receive audio recordings to aid practice daily at home. The home meditation exercises session will take from 10 to 30 min. and will be based on the program developed by Kabat-Zinn (27).
The education program (group 3) aimed at improving self-management and social identification, will constitute the control group (40). Participants will receive information on relevant topics including pain and symptom management, stress, sleep, eating habits, mental health problems, communication skills and physical activity by a qualified health professional. They will have the opportunity to discuss their thoughts and experiences with the other patients in the group with the aim of strengthening social identity and support, which in turn is expected to foster more healthy management (41). This is regarded as a relevant control group because self-management programs may be cost-effective alternatives to other treatments, with likely effects on psychological well-being, but not on pain and disability (42).

4.1.5 Organization of the groups
The two active treatment programs and the education program all consist of eight four-hour group sessions (eight subjects) during an eight-week period. All therapists will before they are considered qualified receive clinical training within the specific treatment modality during a three month period including two 2-day workshops led by a certified trainer in each field. Each treatment session will be videotaped. A random selection of videotaped sessions will be scored by two experts to establish treatment variance, treatment adherence and treatment competence. Inter-rater reliability will be assessed.

4.1.6 Data collection

Diagnostic status and assessment before inclusion: The four multidisciplinary pain centers have participated in 16 national meetings over the past four years were a common protocol for examining and assessing patients with chronic pain was developed. This is described in a recent study (8) which includes standard examination of neuropathic pain (30) and fibromyalgia (43). Patients will also be examined by a clinical psychologist for concurrent comorbid psychiatric disorder according to Structured Clinical Interview for DSM-5 (44).

Primary outcome measure: Pain intensity measured by the Brief Pain Inventory including four 0-10 numerical rating scales; pain now, least pain, worst pain, average pain (45).

Primary process measures: Attentional functioning will be measured using the attention network test which is specifically designed to measure orienting, alerting and executive attention which can be reported the patients computer and lasts about 15 min (46).

Secondary outcomes: Physical function and mental health measured by the SF-36 health survey (47), pain catastrophizing (48), fatigue (49), insomnia severity (50), subjective everyday memory problems (51), anxiety and depression (52), pain related beliefs and attitudes about sleep (53) and the five factor mindfulness questionnaire (54).

Measure points: Primary outcome, attentional functioning and secondary outcomes will be assessed before treatment, end of treatment at eight weeks, 16 weeks, 32 weeks, and 52 weeks follow up from the patients ´computers after automatic cell-phone call. This is a privacy data security trusted reporting system shown by our research group to be feasible (34). Adherence to mindfulness will be assessed weekly by mobile SMS.

Tertiary outcome measures: Changes in work participation will be analyzed from time of recruitment through one year. The first variable will be dichotomous and defined as participation in competitive work > day (7.5 hours) per week on average over 8 weeks. Days of paid work will be used as total number of days worked (continuous variable) in the follow-up period as a cumulative measure of work productivity. The data will be collected from the register of the Norwegian Labour and Welfare Administration (NAV).

Cost-effectiveness and cost-utility will be assessed from a health service perspective and a societal perspective. The health service perspective will include intervention costs (assessment and treatment) and additional relevant primary and secondary health care costs. A micro-costing approach will be applied for calculation of intervention costs. Data on health service utilization will be collected from national and local registers in addition to a patient reported questionnaire to assure complete and relevant information. The societal perspective will in addition include sick leave/productivity costs based on data from the register of the Norwegian Labour and Welfare. Cost-effectiveness will be assessed by comparing incremental costs to incremental primary and secondary outcomes. For cost-utility, Quality Adjusted Life Years (QALY) will serve as the outcome measure. QALY will be calculated from SF-6D (55) and taking time intervals into account.

Other measures: Age, sex, civil status, education level, work and disability status, smoking, physical activity, diet and lifestyle habits, major life events and frequency (and time) practicing mindfulness.

4.1.5 Statistical power

We calculated sample size based on an assumption of a mean baseline pain intensity of 5.4 with a standard deviation of 2.1 (56) and a 10% reduction in pain intensity in the education group, 20% in the ACT group and 30% in the ACT with mindfulness training group. These improvements may be regarded as minimally important vs moderate changes, respectively (16, 57). For a two-sided test with 5 % significance level and 80% power, we calculated that the number of patients needed to compare ACT with mindfulness to the education group was 58 in each group. Comparing ACT with and ACT without mindfulness training would require 141 in each group, and comparing ACT without mindfulness training to education would require 126 in

each group. We increased group size to 162 participants per group to allow for dropout, to provide equality between groups and for secondary analyses. Both intention to treat and treatment completer analyses will be conducted. A detailed data analysis strategy will be outlined before collecting the data.

4.2. Participants, organization, collaboration and dissemination
The research project will be conducted by a research consortium which will have meetings quarterly, as well as a scientific collaborative group. The role, position and competence of the 17 active partners who have developed this application are listed and described in detail in the application form. One is a user participant (see paragraph 5 below), one is an international partner from Uppsala, Sweden, four are from Helse Midt, three from from Helse Sør-Øst, three from Helse Nord and two from Helse Vest, three have their primary positions at the universities (Trondheim and Oslo), and one is a researcher and a health economist. They will all continue to have an active role in the described project, thirteen as researchers, and thirteen as clinicians, and one as user.

The 13 clinicians who are among the most experienced pain clinicians in Norway are leading psychologists, physicians, and physiotherapists from each of the centers. Five have led ACT and mindfulness training and have published scientific articles on the subjects (58, 59). The head of the multidisciplinary pain centers in the four Norwegian university hospitals, who already meet several times a year within the Norwegian Pain Center Network (homepage smertenettverk.no) will, together with the user participant, constitute the research consortium. At the beginning of the study project, there will be several meetings, one concerning the treatment protocol led by Stiles and Jacobsen (ACT therapy and mindfulness training), one on ICD-10-diagnoses including neuropathic pain and fibromyalgia (Borchgrevink, Stubhaug, Woodhouse), and one about psychiatric and neuropsychological aspects and diagnoses (Stiles, Landmark, Landrø).

4.3. Budget
The budget is shared between the four centers and details are given in the electronic application.

4.4. Plan for activities, visibility, and dissemination
A time period of five years is scheduled for completing the entire project. Details are given in the electronic application. Results will be communicated to researchers, clinicians, patients, user organizations, and the public and politicians/decision makers. The results will be published in international journals with a high impact factor. The research project will be the basis for four PhD-theses. The results will be disseminated to other clinicians and clinics through clinical workshops and lectures, through popular papers in relevant medical, physiotherapeutic and psychological journals, communication on the e-network for Norwegian General Practitioners (Eyr), and through the Norwegian Competence Centre for Complex Symptom Disorders using information leaflets, supervision and conferences. The results will be communicated to user organizations in close collaboration with them. The results will also be communicated to the general population and politicians through articles in newspapers and specific magazines or websites. This may also include meetings with politicians and policy makers or informing the Norwegian health authorities through meetings or informational letters.

Planned scientific papers are:
1. Comparing ACT with and without enhanced mindfulness training to a patient education program: a randomized controlled trial (hypothesis 1 and 2).
2. Does mindfulness training improve attentional processes in chronic pain patients? Secondary analyses from a randomized controlled trial (hypothesis 3 and 4).

3. Are effects of ACT and mindfulness training for chronic pain mediated by changes in attentional processing? Results from a randomized controlled trial (hypothesis 5 and 6).
4. ACT for chronic pain, for whom does it work? Moderators of change in a randomized controlled trial (hypothesis 7 and 8).
5. Patient education or ACT for chronic pain? A cost-effectiveness analyses of a randomized controlled trial (hypothesis 9).
6. The long-term effects of ACT for chronic pain, a three-year follow up from a randomized controlled study (hypothesis 10).

4.5. Plan for implementation

The research consortium ensures that the research study is closely affiliated with the routine clinical practice in all four health regions. Specific researchers and specific clinicians are geographically located in each region to ensure that the recruitment, assessment and treatment of patients are conducted in accordance with the research protocol and can ensure that the study can be implemented immediately. Already in 2023 it should be possible to begin the implementation of new empirical knowledge from this research project into the routine practice of the clinics participating in the study and to offer other pain clinics and rehabilitation centers nationally and internationally, including psychiatric outpatients clinics, concrete ways of implementing this knowledge into their assessment and treatment programs. A great advantage of this research project is that it makes use of practical and specific tools and procedures which are theoretically and empirically founded in cognitive neuroscience and within modern clinical psychology and medicine which makes translation into new clinical procedures convenient.

5. User involvement

The User Committee at St. Olav´s hospital has appointed Anne Lein as the user participant to follow the research field for Department of pain and complex symptom disorders. She accepted in 2017 to be engaged in the planning process and be part of the Research Consortium that will meet four times a year (see paragraph 4.2 above). She proposed that one of the groups should be mindfulness training, which was accepted. She got the first draft at the same time as the other partners and thereafter she was part of a planning meeting. Besides inclusion of an active user participant in the Research Consortium monitoring the study, "The Norwegian society for chronic pain patients" has been informed with an overview of the project in Norwegian, and their leader Turid Leganger has responded positively. During the project period four additional user representatives, one in each region, will be selected by User organizations. They will be involved in all stages of planning and implementation as well as during results analyses and results communication. These four representatives will have formal meetings with the Research Consortium and members of the Scientific network group at treatment start and each spring and each autumn during the entire project period.

6. Ethical considerations

The research project will be submitted to a Regional Committee for Ethics in Medical Research and will be conducted in accordance with the declaration of Helsinki and the Principles of Good Clinical Practice. Participation in the study will be based on informed consent including willingness to be videotaped. Thorough information will be provided both orally and in writing to potential participants. None of the treatments are considered to be harmful. If negative side effects occur, they will be reported in detail in the patient-specific study file and in the hospital record. They will also be reported in scientific publications. If a serious adverse event or a serious side effect occurs, the patient will be advised to resign from the study and will be given adequate attention and treatment. Negative side effects/serious adverse events will also be reported to relevant health authorities Data used for research purposes will be stored without personal identifying information for five years after the end of the study. Participants will be

informed of data storage procedures. The study will be registered at clinicaltrials.gov and helsenorge.no.

7. References

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