Protocol: **Evaluation of a mind-body based application for the treatment of chronic/persistent pain.**

Principal Investigator:
Cynthia J Thomson
Faculty of Health Science
University of the Fraser Valley
45190 Caen Avenue
Chilliwack, BC Canada V2R 0N3
Tel: 604-792-0025 x2518
Email: cynthia.thomson@ufv.ca

Co-Investigator: Luisa V. Giles;
Research Assistant: Hanna Pahl

University of the Fraser Valley
ID: #1008820
NCT:
Protocol version date: October 12, 2021

Evaluation of a mind-body based application for the treatment of chronic/persistent pain.

Background

Pain becomes chronic when it persists beyond the typical time it would take for tissue to heal (usually 3 months), and therefore chronic pain is commonly defined as consistent or recurrent pain that lasts for more than three months (Treede et al., 2015). Chronic pain affects approximately 1 in 5 Canadians (Health Canada, 2021; Schopflocher et al., 2011) and is among the leading causes of years lived with disability globally (GBD, 2016). Chronic pain can be classified into sub-categories dependent on either location of the pain (e.g., visceral, headache/orofacial, musculoskeletal), the etiology of the pain (e.g., cancer, post-surgical, neuropathic), or its features (e.g., primary pain) (Treede et al., 2015).

The biopsychosocial model of pain illustrates that pain is both a sensory and emotional experience (Darnall et al., 2017). Pain has been described as a subjective perception of sensory information that can be influenced by genetics, learned experience, psychological state, and sociocultural influences (Gatchel et al., 2007). Many treatment modalities focus on the sensory or physical aspects of pain, but there is much less emphasis on treating the emotional experience of pain, and pain specific training for health professionals is lacking (Darnall et al., 2017). Emerging studies on interdisciplinary interventions that address the physical, emotional, and cognitive aspects of pain have reported small to medium positive effects (e.g., Bujak et al., 2019; Joypaul et al., 2019). Interventions employing mindfulness training reported small effect sizes for reductions in pain intensity, along with improvements in quality of life, although the quality of evidence analyzed was low (Hilton et al., 2017). A meta-analysis on interventions employing neurophysiological pain education, which uses cognitive behavioural techniques (CBT) to re-conceptualize beliefs about pain, reported small to moderate effect sizes for pain reduction in patients with chronic lower back pain (Tegner et al., 2018). Similarly, moderate effect sizes were found in studies employing CBT in patients with chronic low back pain (Hoffman et al., 2007).

Interventions that focus on pain education, mindfulness training, and CBT do not involve physical manipulations, and as such there is an opportunity to provide care remotely or through online or mobile-application-(app)-based programming. A recent meta-analysis reviewed seven studies on app-based interventions for chronic pain and found significant (albeit small) improvements in pain intensity (Pfeifer et al., 2020). Other online or mobile app-based interventions for chronic pain in elderly and adolescents have reported improvements in pain intensity and emotional functioning (Shaygan & Jaberi, 2021) and improvements in awareness of pain response (Berman et al., 2009).

A mobile app informed by the biopsychosocial model of pain that employs a "mind-body" approach was evaluated for quality of self-management support functions specific to chronic pain. Mind-body medicine considers the interactions between the brain and body and considers how emotional, cognitive, and social factors can influence health (e.g., Morone & Greco, 2007). The mind-body app that we explore in the current trial scored the highest of the 19 apps evaluated in both number of self-management functions addressed within the app and scored among the highest in overall app quality as measured by a standardized rating scale (Mobile App Rating Scale) (Devan et al., 2019). To our knowledge, this mobile app has not previously been independently evaluated to determine its efficacy in the treatment of chronic pain. The mind-body app encompasses many of the modalities described above, including

mindfulness training through meditation, CBT through brain training exercises and journaling, and pain education through expert interviews and recorded microlessons. We aimed to investigate the efficacy of the mind-body based mobile app in the treatment of chronic pain using a randomized control trial that involved 6-weeks of regular app usage compared to a usual care, wait-listed control group.

Hypotheses

i) Participants in the intervention group will report a greater reduction in pain intensity compared to control participants.
ii) Participants in the intervention group will report improvements in pain catastrophizing, pain interference, and quality of life.
iii) Changes in pain intensity will be correlated with frequency of app usage.

Objectives:

i) To investigate the efficacy of a mind-body based mobile app on the experience of chronic pain relative to a waitlisted control group. Outcomes include self-reported measures of pain intensity, perceptions/thoughts about pain, quality of life, and/or functional ability.
ii) To explore whether frequency of app usage is associated with changes in pain intensity and interference.
iii) To explore whether changes (if any) in pain intensity and interference persist six weeks post-trial completion.

Primary outcome: Pain intensity as measured using the Brief Pain Inventory (BPI).

Secondary outcomes:

a. The following additional measures will be compared between the intervention and control group:
    - Pain intensity as measured by the PROMIS Pain Severity short form measures severity over a 7 day time period.
    - Pain interference as measured by the PROMIS Short Form ((PROMIS Health Organization and Cooperative Group, 2012); (Kean et al., 2016).
    - Pain interference as measured by items in the BPI (Cleeland & Ryan, 1994).
    - Thoughts about pain as measured by Pain Catastrophizing Scale (PCS) score (Sullivan et al., 1995).
    - Quality of life as measured by the short-form (SF)-12 (Ware et al., 1996)
    - Depression, anxiety, and stress as measured by the DASS-21 (Lovibond & Lovibond, 1995).
    - Medication use.
b. The following exploratory analyses will be performed on the intervention group data:
    - Relationship between all outcomes and frequency of app usage in the intervention group.
    - 12-week follow-up analysis (6 weeks post trial end) to determine whether changes (if any) persist.

Methods

Study Design: This is a parallel group randomized control trial. Participants meeting eligibility criteria at pre-trial self-report screening will be invited to participate in the study. Participants who provide informed consent, complete the baseline data collection, and qualify for study inclusion will be randomized to either an intervention group (mind-body app usage for 6-weeks) or a wait-listed control (usual care). Randomization will be stratified on gender and pain intensity.

Participants

Inclusion: Participants aged 18 to 75 years who have non-malignant chronic or persistent pain. Chronic pain is generally defined as persistent pain that has lasted for more than 3 months (Treede et al., 2015). Our study will include participants that have had ongoing pain for at least 6 months, and participants must experience pain at least half the days in the last 6 months (Deyo et al., 2014). Pain can include bodily pain or head pain (migraine/headache). According to the classifications described above by Treede et al., (2015), our study includes participants with primary chronic pain, head/orofacial pain, visceral pain, post-surgical, and musculoskeletal pain.

Exclusions: The following participants are excluded from participation.
Self-reported history of any of the following:

- Psychotic illness or manic episode
- Substance use disorder or problematic substance use within 6 months of start date
- Metastasizing cancers
- Cognitive impairment (that could interfere with using the application)
- Previous experience with the mind-body app under study.

Procedures

Participants qualifying for study inclusion will be randomized to either an intervention group (mind-body app) or a control group (usual care, wait-listed). Randomization will be stratified on pain intensity on average (from Brief Pain Inventory, item that inquires about pain intensity on average) and gender. We decided to include gender rather than sex for data collection and randomization. Few clinical trials in Canada collect data based on gender, and there are numerous ways that gender may impact pain experience (Boerner et al., 2018; Welch et al., 2017). Randomization method will involve computer-generated block randomization to create varying block sizes of 4 and 8. We will run the trial in cohorts (run in series) with rolling recruitment. First cohort will start the trial October 15th, 2021 (randomized on October 14th, 2021). The anticipated start date for the second cohort is January, 2022 (randomized immediately before cohort start). If we meet our targeted sample size with two cohorts, we will stop recruitment. If we do not have a sufficient sample, we will run a third cohort in Spring, 2022. Data will not be analyzed until the final cohort has complete the 12-week follow-up.

Intervention: Participants in the intervention group will be provided 6-weeks of free access to a mind-body based app. The app includes activities that are evidence-based and informed to treat

the biopsychosocial model of pain. The app is self-directed and includes activities in brain training (cognitive behavioural therapy), meditation, pain education, and expressive writing (journaling). The app also includes links to podcasts that include interviews with scientific experts in chronic pain, pain psychologists, and recovery stories. At the start of the trial participants will be given a brief (<5 min) introductory video to orient them to the app and provide guidelines and tips. Participants will be asked to engage with the app daily or at minimum 4 times per week. A weekly frequency log (during weeks 2, 3, 4, 5, and 6) will be sent to participants via email (with a link to survey monkey) to record number of times they used the app in the previous 7 days. During the trial, participants are asked to continue with usual care for pain treatments (in addition to app usage).

Control: Participants in the control group will be made aware that they are in the control group as they await access to the app following completion of the trial. They are asked to continue with their usual care for pain treatments over the 6-week trial. A weekly email will be sent to control participants (with a link to survey monkey), to include similar frequency of contact with the research team, and to record any changes (if any) in usual care treatments.

Measures
All participants (control and intervention) will complete baseline questionnaires (detailed below) and a follow-up set of questionnaires at 6 weeks (same as baseline, minus the demographics and pain history sections). All questionnaires and logs will be completed through surveymonkey.com. To link pre- and post-surveys along with frequency logs, participants will be given a unique alphanumeric identifier. We will do an additional follow-up survey at 12 weeks in the intervention group. This survey will be similar to the survey at 6 weeks, but will also inquire whether participant continued with app usage.

Measures:
The questionnaires will include the following:

1. Demographics: We will collect data on gender, age, socioeconomic status (education, income), residence, relationship status, dependents, employment status.
2. Pain history: Participants will provide information on their pain condition. This will include location, diagnosis, date of onset, average frequency, changes in employment due to pain. Other details regarding pain are captured in the questionnaires that follow.
3. Brief Pain Inventory Short Form (BPI-SF) - this includes items about location of pain, intensity of pain, current treatments, and interference with daily activities (Cleeland & Ryan, 1994)
4. PROMIS Pain Intensity Scale (Adult Short form) - 3 items (PROMIS Health Organization and Cooperative Group, 2012).
5. PROMIS Pain Interference Scale (Adult Short form) - 8 items (PROMIS Health Organization and Cooperative Group, 2012).
6. Pain Catastrophizing Scale (Sullivan et al., 1995).
8. DASS-21 (Depression, Anxiety, Stress Scale) - 21 items (Lovibond & Lovibond, 1995).
9. QoL questionnaire- SF 12 (Ware et al., 1996).

Data analysis

Power analysis: We estimated a moderate effect size of $f = 0.3$ (Cohen's $d = 0.6$). A meta-analysis of mobile app-based interventions for the treatment of chronic pain (Pfeifer et al., 2020) reported a small effect at Cohen's $d = 0.4$, but the content of the apps was highly variable and not all included pain education and/or CBT exercises. Another meta-analysis on psychological interventions that included CBT compared to wait-listed controls reported a Cohen's $d = 0.62$ (Hoffman et al., 2007). Using G-power (Erdfelder et al., 2009) calculation with an estimated power of $f = 0.3$, a sample size of $n = 90$ would be required to achieve 80% power (at *alpha* = .05). We aimed to enroll $n = 100$ participants in total.

Statistical analysis: Data will be analyzed using repeated measures analysis of co-variance (ANOVA) with baseline data as a covariate, intervention *vs.* control as between-group factors, and variable of interest (e.g., pain intensity) as the dependent variable for the primary analysis. It is recommended that randomized controlled trials employ ANCOVA rather than paired t-tests or repeated measures ANOVA (Egbewale et al., 2014).

References

Berman, R. L. H., Iris, M. A., Bode, R., & Drengenberg, C. (2009). The Effectiveness of an Online Mind-Body Intervention for Older Adults With Chronic Pain. *Journal of Pain*, *10*(1), 68–79. https://doi.org/10.1016/j.jpain.2008.07.006

Boerner, K. E., Chambers, C. T., Gahagan, J., Keogh, E., Fillingim, R. B., & Mogil, J. S. (2018). Conceptual complexity of gender and its relevance to pain. In *Pain* (Vol. 159, Issue 11, pp. 2137–2141). Lippincott Williams and Wilkins. https://doi.org/10.1097/j.pain.0000000000001275

Bujak, B. K., Regan, E., Beattie, P. F., & Harrington, S. (2019). The effectiveness of interdisciplinary intensive outpatient programs in a population with diverse chronic pain conditions: a systematic review and meta-analysis. *Pain Management*, *9*(4). https://doi.org/10.2217/pmt-2018-0087

Cleeland, C. S., & Ryan, K. M. (1994). Pain assessment: global use of the Brief Pain Inventory. In *Annals of the Academy of Medicine, Singapore* (Vol. 23, Issue 2).

Darnall, B. D., Carr, D. B., & Schatman, M. E. (2017). Ethics forum: Pain psychology and the biopsychosocial model of pain treatment: Ethical imperatives and social responsibility. In *Pain Medicine (United States)* (Vol. 18, Issue 8, pp. 1413–1415). Oxford University Press. https://doi.org/10.1093/pm/pnw166

Devan, H., Farmery, D., Peebles, L., & Grainger, R. (2019). Evaluation of Self-Management Support Functions in Apps for People With Persistent Pain: Systematic Review. In *JMIR mHealth and uHealth* (Vol. 7, Issue 2). JMIR Publications Inc. https://doi.org/10.2196/13080

Deyo, R. A., Dworkin, S. F., Amtmann, D., Andersson, G., Borenstein, D., Carragee, E., Carrino, J., Chou, R., Cook, K., Delitto, A., Goertz, C., Khalsa, P., Loeser, J., MacKey, S., Panagis, J., Rainville, J., Tosteson, T., Turk, D., von Korff, M., & Weiner, D. K. (2014). Report of the NIH task force on research standards for chronic low back pain. *Journal of Pain*, *15*(6), 569–585. https://doi.org/10.1016/j.jpain.2014.03.005

Egbewale, B. E., Lewis, M., & Sim, J. (2014). Bias, precision and statistical power of analysis of covariance in the analysis of randomized trials with baseline imbalance: A simulation study. *BMC Medical Research Methodology*, *14*(1). https://doi.org/10.1186/1471-2288-14-49

Erdfelder, E., FAul, F., Buchner, A., & Lang, A. G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behav Res Methods*, *41*(4). https://doi.org/10.3758/BRM.41.4.1149

Erratum: Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016 (The Lancet (2017) 390(10100) (1211–1259) (S0140673617321542) (10.1016/S0140-6736(17)32154-2)). (2017). In *The Lancet* (Vol. 390, Issue 10106). https://doi.org/10.1016/S0140-6736(17)32647-8

Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The Biopsychosocial Approach to Chronic Pain: Scientific Advances and Future Directions. *Psychological Bulletin*, *133*(4). https://doi.org/10.1037/0033-2909.133.4.581

Health Canada. (2021). *Canadian Pain Task Force Report: March 2021: An Action Plan for Pain in Canada*.

Hilton, L., Hempel, S., Ewing, B. A., Apaydin, E., Xenakis, L., Newberry, S., Colaiaco, B., Maher, A. R., Shanman, R. M., Sorbero, M. E., & Maglione, M. A. (2017). Mindfulness

Meditation for Chronic Pain: Systematic Review and Meta-analysis. *Annals of Behavioral Medicine*, *51*(2), 199–213. https://doi.org/10.1007/s12160-016-9844-2

Hoffman, B. M., Papas, R. K., Chatkoff, D. K., & Kerns, R. D. (2007). Meta-analysis of psychological interventions for chronic low back pain. *Health Psychology*, *26*(1), 1–9. https://doi.org/10.1037/0278-6133.26.1.1

Joypaul, S., Kelly, F., McMillan, S. S., & King, M. A. (2019). Multi-disciplinary interventions for chronic pain involving education: A systematic review. In *PLoS ONE* (Vol. 14, Issue 10). https://doi.org/10.1371/journal.pone.0223306

Kean, J., Monahan, P. O., Kroenke, K., Wu, J., Yu, Z., Stump, T. E., & Krebs, E. E. (2016). Comparative responsiveness of the PROMIS pain interference short forms, brief pain inventory, PEG, and SF-36 bodily pain subscale. *Medical Care*, *54*(4). https://doi.org/10.1097/MLR.0000000000000497

Lovibond, P. F., & Lovibond, S. H. (1995). The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behaviour Research and Therapy*, *33*(3). https://doi.org/10.1016/0005-7967(94)00075-U

Morone, N. E., & Greco, C. M. (2007). Mind-body interventions for chronic pain in older adults: A structured review. In *Pain Medicine* (Vol. 8, Issue 4, pp. 359–375). https://doi.org/10.1111/j.1526-4637.2007.00312.x

Pfeifer, A. C., Uddin, R., Schröder-Pfeifer, P., Holl, F., Swoboda, W., & Schiltenwolf, M. (2020). Mobile application-based interventions for chronic pain patients: A systematic review and meta-analysis of effectiveness. In *Journal of Clinical Medicine* (Vol. 9, Issue 11). https://doi.org/10.3390/jcm9113557

Schopflocher, D., Taenzer, P., & Jovey, R. (2011). The prevalence of chronic pain in Canada. *Pain Research and Management*, *16*(6). https://doi.org/10.1155/2011/876306

Shaygan, M., & Jaberi, A. (2021). The effect of a smartphone-based pain management application on pain intensity and quality of life in adolescents with chronic pain. *Scientific Reports*, *11*(1). https://doi.org/10.1038/s41598-021-86156-8

Sullivan, M. J. L., Bishop, S. R., & Pivik, J. (1995). The Pain Catastrophizing Scale: Development and Validation. *Psychological Assessment*, *7*(4). https://doi.org/10.1037/1040-3590.7.4.524

Tegner, H., Frederiksen, P., Esbensen, B. A., & Juhl, C. (2018). Neurophysiological Pain Education for Patients with Chronic Low Back Pain. In *Clinical Journal of Pain* (Vol. 34, Issue 8). https://doi.org/10.1097/AJP.0000000000000594

Treede, R. D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., Cohen, M., Evers, S., Finnerup, N. B., First, M. B., Giamberardino, M. A., Kaasa, S., Kosek, E., Lavand'homme, P., Nicholas, M., Perrot, S., Scholz, J., Schug, S., Smith, B. H., … Wang, S. J. (2015). A classification of chronic pain for ICD-11. In *Pain* (Vol. 156, Issue 6, pp. 1003–1007). Lippincott Williams and Wilkins. https://doi.org/10.1097/j.pain.0000000000000160

Ware, J. E., Kosinski, M., & Keller, S. D. (1996). A 12-Item Short-Form Health Survey: Construction of Scales and Preliminary Tests of Reliability and Validity. *Medical Care*, *34*(3). https://doi.org/10.1097/00005650-199603000-00003

Welch, V., Doull, M., Yoganathan, M., Jull, J., Boscoe, M., Coen, S. E., Marshall, Z., Pardo, J. P., Pederson, A., Petkovic, J., Puil, L., Quinlan, L., Shea, B., Rader, T., Runnels, V., & Tudiver, S. (2017). Reporting of sex and gender in randomized controlled trials in Canada:

a cross-sectional methods study. *Research Integrity and Peer Review*, *2*(1). https://doi.org/10.1186/s41073-017-0039-6