Cover page

Title: MBCT for Cancer Patients in Follow-Up

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Mindfulness-based cognitive therapy for pain in cancer patients after primary treatment: An open implementation trial

Background

International research shows that untreated or undertreated pain among cancer patients after completion of therapy is a common problem with substantial negative impact on the patients' quality of life and mental and physical function [1-4]. A summary of literary reviews estimates that 19-41% experience pain between six months and five years after ended treatment [5]. While there are still relatively few Danish studies, this appears also to be the case in Denmark. Thus, in a national cohort of 3,343 women treated for breast cancer, we found that, respectively, 33% and 20% of the women reported pain "almost every day" or more 15 months and 7-9 years after treatment [6]. Based on a pain audit conducted at the Oncology Department at Aarhus University Hospital (AUH), we found that 50% had experienced pain in the past week, and that half of these patients had experienced pain for a month or more [7]. Among patients in follow-up care, 38% had experienced pain in the past week. A subsequent audit, at the Oncology Department, showed this percentage to be roughly unchanged (35%) [8], despite greater focus on education and patient interviews about pain. Research suggests that the extent of the problem may be due to 1) failure to identify patients with pain, 2) lack of or ineffective pharmacological pain therapy, and 3) adverse reactions to pharmacological pain therapy [9]. The first problem may be attributable to a lack of systematic screening for pain in oncology [10]. Our audit data shows that approx. 20% of patients had not spoken to hospital staff and that 60% had not spoken with their general practitioner about their pain [7, 8]. The second problem relates to the issue that even when patients with pain are identified and receive pharmacological pain therapy, many continue to experience pain [11, 12]. This is due, in part, to complex pain etiology, where cancer patients and cancer survivors' pain may be due to both the effects of the actual cancer and to the negative sequelae of the different cancer treatment's modalities, including surgery, chemotherapy, hormonal therapy and antibody therapy [3, 13]. Additionally, many cancer patients experience neuropathic pain [14, 15], which is difficult to treat pharmacologically, as confirmed by our data [7]. Finally, pharmacological therapy can result in adverse reactions, including memory and concentration difficulties, constipation, symptoms of depression, impaired reproductive function and sexual dysfunction [16]. These challenges have increased interest in psychological pain therapy. The benefits of psychological pain therapy include: 1) that psychological treatments are presumed to have little or no adverse effects; 2) that pain is a multidimensional phenomenon that involves complex connections between biological, psychological and social processes [17]; and 3) that newer meta-analytical studies document that psychological interventions are effective on both chronic pain in general [18], such as cancer-related pain, including among patients with mixed cancer forms [19] and, as we have demonstrated most recently, breast cancer patients [20]. Among the available methods of psychological intervention, mindfulness-based interventions (MBI) are of particular interest. MBI appears to be particularly relevant for pain, as mindfulness focuses, through different meditation exercises, on concentrating attention on here-and-now experiences and supporting new ways of addressing physical sensations and emotional discomfort, characterized by greater acceptance and openness [21]. MBI has been shown effective in treatment of nonmalignant chronic pain [22-24].

Objectives

Aarhus University Hospital has adopted the reduction of late effects of cancer treatment as one of its core strategies [25]. As supported by the results of the pain audits at the Oncology Department at AUH completed

in 2011 [7] and 2014 [8], as well as in the nationwide cohort study of Danish women treated for breast cancer [6], persistent pain is a significant problem for many former cancer patients and survivors. We previously presented documentation on the effect on cancer-related pain of psychological interventions in general [20] and of mindfulness-based cognitive therapy (MBCT) in specific [26]. We therefore wish to extend the results of the previously published explanatory trial of MBCT for pain in cancer survivors [26] by conducting an open pragmatic trial focusing on the real-life implementation of MBCT in an oncology department and the generalizability in the everyday clinical setting of the results previously found for breast cancer survivors to all cancer patients who have completed their primary treatment and experience clinically significant pain. Specifically, the objectives of the present study are: 1) to executing the practical implementation in an oncology department of MBCT for patients who have completed their primary treatment and experience significant cancer- and cancer-treatment-related pain, 2) to evaluate effects on pain and well-being, 3) to explore patient satisfaction with the intervention offered, and 4) to explore possible organizational and individual physical, mental and socio-economic barriers for implementation in relation to drop-outs.

Methods

Participants

Inclusion criteria: Adult (≥18 years old) cancer patients who have completed primary cancer treatment (excluding long-term anti-hormone therapy, e.g., tamoxifen) at the Oncology Department at Aarhus University Hospital and who are experiencing moderate to severe pain measured as a score of ≥4 (0-10 NRS) on the following pain dimensions: a) pain intensity, b) pain burden, c) pain impact (function) and/or d) perceived need for help with pain management. Exclusion criteria: <18 years of age, not yet completed chemo or radiation therapy, metastases, and serious psychiatric diagnosis, e.g., psychosis. Patients seen by all four diagnosis teams at the Oncology Department at AUH are screened for pain (0-10 NRS) in connection with their final consultation with the oncologist. Patients with a pain score of ≥ 4 on one or more of the four pain dimensions questions receive a folder describing MBCT and the treatment plan and are encouraged to contact the MBCT team for more information and scheduling of an interview. If the patient, after initial information either by phone or after the first interview decline the offer to participate, but are willing to be contacted for the purpose of gathering more information about their reasons for not participating, we will send them a brief questionnaire concerning their pain and their reasons for choosing to decline the offer, to complete online. They are also asked to give their permission to collect the same information after three months. All data are collected and registered with REDCap [27], a high data security project administration system administered by Aarhus University's Clinical Trial Unit. Based on the 2014 pain audit results, we anticipate that of approx. 3,250 annually completed treatment plans across diagnoses, about 400 cancer patients will experience clinically significant pain (NRS score of ≥ 4 on one out of four pain dimensions) after completed primary treatment. From our experience with psychological treatment of cancer patients, we conservatively anticipate that approx. 35% will accept the offer and that 15% will drop out early, resulting in approx. 120 patients per year. It should be noted that the true extent of the need for psychological intervention for pain in the department is yet unknown. The present implementation project will help to determine this.

Intervention

As patients with significant pain are identified and accept the offer of receiving MBCT for pain, they will be consecutively included in groups of 12-20 participants. The patients will participate in eight weekly two hour

group sessions and will be asked to do an additional 45 minutes of daily training at home. The participants will be asked to record their home training to allow assessment of their adherence to the intervention. The program corresponds to the manualized MBCT program [28], but with adaptations that take into account the special needs of cancer patients [29, 30], including somewhat shorter sessions, shorter yoga exercises, and the omission of the all-day session. The sessions include psychoeducation and formalized mindfulness exercises with focus on the participants' here-and-now experience of their pain. According to the existing guidelines from Oxford Mindfulness Centre (OMC), Oxford University, where MBCT was developed, the instructor's professional and regular training, as well as supervision in MBCT, are critical for the quality of MBCT as intervention [31]. The instructors' training and supervision adhere to the OMC guidelines.

Evaluation

The aim of the present project is to evaluate the *practical implementation* of MBCT, with focus on: 1) the observed effects on pain (*primary outcome parameter*), 2) effects on quality-of-life (QoL) and on other cancer and cancer-treatment-related late effects associated with pain (*secondary outcome parameter*), 3) possible barriers for continued participation in the program (drop-out), 4) patient experience and satisfaction with the intervention and its organizational/practical implementation, 5) staff's experience of screening procedure and implementation, and 6) collection of data for use in the evaluation of effects, costs, and savings. For use in the evaluation, the patients complete questionnaires prior to the first session (T1), immediately after the last session (T2), and at a six-month follow-up (T3).

Instruments

The patient-reported measures at T1, T2, and T3 include:

1) T1-T3: Pain measures (pain intensity, pain burden, pain impact (function), and the need for help with pain management) (0-10 pt. NRS). The primary effect measure is pain intensity, which has been shown a valid measure of pain in cancer patients [32].

2) T1-T3: The patients' pain profile is assessed using a list of pain descriptors from the McGill Pain Questionnaire [33] and the *Douleur Neuropathique en 4 Questions* [Neuropathic Pain in Four Questions] [34]. The descriptors cover somatic, visceral, neuropathic and affective pain [35].

3) T1-T3: General QoL is measured using the EQ5D [36]. Other secondary outcomes include: depressive symptoms (Beck's Depression Index [37]), sleep difficulties (the Insomnia Severity Index [38]), cancer-related QoL (EORTC-QLQ-C30 [39, 40]), fear of cancer recurrence (FCRI-SF [41]), dispositional mindfulness (the Five Facet Mindfulness Questionnaire [42]), and self-compassion (the Self-Compassion Scales [43]).

4) T2-T3: Patient-experienced satisfaction with the treatment plan (5-pt. Likert Scale) and open questions concerning any experienced difficulties and challenges in connection with participation in the treatment plan.

5) For use in planned assessments of costs and savings, the participants are asked for their permission to collect relevant data from national and local registries. On the end of the project period, we will also explore the staff's impressions of the screening procedures and implementation with a brief questionnaire. Non-participants who have agreed to be contacted for further information will be contacted by email or phone and answer: 1) the four pain dimensions (at time points corresponding to T1-T3) and 2) a questionnaire with closed and open questions concerning their reasons for not participating, e.g., time, geography, attitude

towards psychological pain intervention (barriers) and what help, if any, they receive to manage their pain, e.g., pain medication, physiotherapy, psychological help, own activities (resources) (T1).

Statistical analysis

Intention-to-treat (ITT) analyses will be conducted with Multilevel Linear Models (MLMs). In the analysis, we will focus on 1) changes over time (T1-T3) in pain measurements. We will also compare patients who experience statistically (Reliable Change Index) [44] and clinically significant changes (NRS ≥2) [45] with the remaining patients. In the secondary analyses, we will focus on 1) effects on QoL and other secondary outcomes and explore the possible moderating influence of demographic and clinical background variables to changes in pain. Additionally, we will investigate 3) the staff's impressions of screening procedures and implementation. Furthermore, 4) nonparticipants will be studied with regard to changes in pain and reasons for not participating (barriers and resources). 5) If the implementation is deemed successful, cost analyses will be conducted on the basis of outcomes and registry data concerning health care utilization.

Dissemination

The results will be sought published in a report focusing on: 1) the effects of the implemented program on pain, 2) the effects on QoL and other secondary outcomes associated with pain, e.g., depressive symptoms, sleep disturbance, 3) the reasons for patient nonparticipation, 4) patient satisfaction with the treatment program, and 5) the staff's experience of screening procedures and implementation. Furthermore, if successful, a further report will be produced, focusing on 6) costs and possible savings obtained by implementing the intervention as standard treatment for post-treatment pain in the department.

Perspectives

Persistent pain is a late effect of cancer and cancer treatment that constitutes a significant problem for the individual patient, health services and society [2, 46]. Consequently, the need exists for available evidence-based treatments for such problems to be implemented in health services [25, 47]. The project is in line with Aarhus University Hospital's desire to develop and implement evidence-based strategies for the prevention and treatment of late effects of cancer and cancer treatment. The analysis of health-economic data from our published RCT [26] showed an average savings in health services consumption (including MBCT expenses) per patient having completed therapy of approx. DKK 5,421 over an eight-month period. When this data is extrapolated to correspond to one year, savings of DKK 8,131 per participant are achieved, giving net savings for total consumption of health services of about DKK 975,780 per year for 120 patients. As such, the implementation of MBCT as a treatment program for post-treatment pain in cancer patients is expected to be cost-neutral, at minimum, while *at the same time*, expecting a clinically significant reduction in pain among those patients who accept the treatment plan.

Ethics

We will adhere to the rules and guidelines as formulated by the Helsinki Declaration-II and the Danish Data Protection Agency. Withdrawal from the project or otherwise will have no influence on the patients treatment. The Regional Ethical Committee has evaluated the project as a questionnaire survey which does not involve human biological material and therefore does not need approval from the Committees, Act number 1083 of 15th September 2017, section § 14 (2) (appendix 1).

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