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CANCER-RELATED FATIGUE

with an emphasis on understudied populations in psychosocial oncology
HANNEKE POORT

CANCER-RELATED FATIGUE

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About the cover
In the poem “Hope is the thing with feathers” by Emily Dickinson (1830-1886), the speaker creates a metaphor of hope through a little bird that perches in the soul. There, it sings wordlessly and without pause in the face of the strongest wind and most powerful storm.

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CANCER-RELATED FATIGUE
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Hanneke Poort
geboren op 2 september 1987
te Roermond
Promotoren
Prof. dr. W.T.A. van der Graaf
Prof. dr. G. Bleijenberg
Prof. dr. J.A. Knoop (AMC)

Copromotor
Dr. C.A.H.H.V.M. Verhagen

Manuscriptcommissie
Prof. dr. E. van Leeuwen (voorzitter)
Prof. dr. J.A. Witjes
Prof. dr. C.C.D. van der Rijt (Erasmus MC)

Paranimfen
Harriët Abrahams
Simône de Mare-Langenberg
Voor mijn ouders
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CHAPTER 1

GENERAL INTRODUCTION
Expert Center for Chronic Fatigue

The studies reported in this thesis are carried out at the Expert Center for Chronic Fatigue (ECCF) in the Netherlands. Until December 2016, the ECCF was affiliated with the Radboud university medical center (Radboudumc) in Nijmegen. Since January 2017, the ECCF is affiliated with the VU University Medical Center (VUmc) and the Academic Medical Center (AMC) in Amsterdam. The ECCF originally focused on studying chronic fatigue syndrome and successfully developed and tested a cognitive-behavioural intervention for patients with chronic fatigue syndrome [1-7]. The first studies on cancer-related fatigue (CRF) at the ECCF have been performed in 1996 in collaboration with the Department of Medical Oncology at the Radboudumc. There are various definitions of CRF, but the most frequently used definition is the one formulated by the National Comprehensive Cancer Network, which defines fatigue as “a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” [8]. CRF is a frequent, almost universal symptom in patients with cancer, yet it is a problem that is highly underreported, underrecognized and also undertreated [9-11]. Over the past 20 years, the ECCF performed several studies on the prevalence, impact, and treatment of CRF in different cancer populations that will be described below.

Fatigue after cancer treatment with curative intent

The initial CRF studies at the ECCF dealt with the presence and course of CRF in disease-free cancer patients and demonstrated that fatigue is a serious and persistent problem for at least a quarter of these cancer survivors [12]. Several psychological and behavioural factors were associated with the persistence of fatigue complaints in a longitudinal study [12]. These findings have led to the development of an explanatory model, in which precipitating and perpetuating factors of CRF in disease-free cancer survivors were distinguished. The precipitating factors include cancer and its treatment and serve as triggers for fatigue. Upon completion of cancer treatment, however, other factors are responsible for the persistence of fatigue. These perpetuating factors include inappropriate coping skills, fear of cancer recurrence, dysfunctional fatigue-related cognitions, deregulated sleep-wake patterns, deregulated activity patterns, low social support and negative interactions. Based on this explanatory model, a cognitive-behavioural intervention for CRF in disease-free cancer survivors was developed and tested in comparison with usual care in a randomised controlled trial (RCT) [13]. The intervention proved to be effective in reducing CRF and functional impairments and positive intervention effects were sustained up to two-years follow up [14]. However, treatment capacity is limited, as delivery of this clinic-based intervention requires a significant amount of therapist time. To extend treatment options, a web-based version of this intervention requiring less therapist time has been developed recently [15]. Efficacy of this web-based intervention has been evaluated.
in an RCT with 132 severely fatigued breast cancer survivors and the findings have been submitted for publication [Abrahams et al., submitted for publication].

**Fatigue during adjuvant cancer treatment**
Given the positive effects of cognitive behaviour therapy (CBT) for severely fatigued disease-free cancer survivors, the subsequent studies by the ECCF aimed to prevent the development of long-term CRF by addressing fatigue during or shortly after adjuvant cancer treatment. A three-armed RCT was designed to examine the effects of CBT and a brief nurse-led intervention focusing on physical activity in comparison with usual care. CBT appeared to be effective, the nurse led intervention not [16]. At one-year follow up, the positive intervention effect of CBT for fatigue was no longer observed [17]. However, it is important to note that participants in this study were not selected on the presence of severe fatigue. Thus, the non-significant findings at long-term follow up might be due to a floor effect. The study authors implied that CBT for fatigue should be offered to patients selected on the presence of severe fatigue, who have a higher chance to benefit from the intervention. In addition to selecting those patients most in need, it seems important to develop interventions that specifically target fatigue as these were more effective in reducing fatigue in adult cancer patients compared to interventions with a more general approach [18].

**Fatigue during cancer treatment with palliative intent**
The next step in CRF research at the ECCF was to study patients with advanced or metastatic cancer receiving cancer treatment with palliative intent. Recently conducted studies by the ECCF investigated the prevalence of CRF in these patients and reported that almost half of the patients (47%) scored above the threshold for severe fatigue [19]. Furthermore, the number of severely fatigued patients increased further along the treatment trajectory, with those receiving further lines of systemic treatment more frequently experiencing severe fatigue compared to patients on first-line treatment. A longitudinal study revealed that fatigue levels remained relatively stable over 6 months’ time [20]. Lastly, the perpetuating factors from the explanatory model of CRF in disease-free cancer survivors were evaluated in the sample of patients with incurable cancer. All factors were correlated with fatigue severity [21]. In addition, a low level of self-reported physical activity and difficulties in accepting the incurable nature of the disease at baseline were predictors of fatigue over time [20].

**Fatigue in understudied populations in psychosocial oncology**
Fortunately, CRF has received more attention in both research and clinical practice in recent years. Yet, the majority of studies on CRF have been performed in patients with common cancer types, such as breast cancer, lung cancer, colon cancer, or prostate cancer and in cancer survivors or patients undergoing cancer treatment with curative intent [22-24]. Comparatively fewer studies have been conducted in samples
of patients with a rare cancer diagnosis or patients undergoing cancer treatment with palliative intent. Despite increased awareness for CRF, these populations remain understudied.

PART I: FATIGUE IN PATIENTS WITH RARE CANCER

Information on the prevalence, impact and correlates of CRF in patients with rare cancers is scarce. As background, a cancer is considered to be rare if the incidence is less than 6 per 100,000 persons diagnosed with it each year (http://www.rarecare.eu/). Despite the rarity of each of the 186 rare cancers, they represent in total about 22% of all annual cancer cases in Europe [25]. The first part of this thesis is concerned with studying CRF in three different groups of patients with rare cancers: cancers occurring in the adolescent and young adult population, gastrointestinal stromal tumors, and chronic myeloid leukemia.

Adolescent and young adult cancer
In the Netherlands, every year approximately 2700 patients are diagnosed with cancer between the age of 18 and 35 years. The discipline of adolescent and young adult (AYA) oncology is an evolving field that has begun to be defined only since the beginning of the new millennium. Historically, these patients, positioned at the intersection of paediatric and adult oncology, have not been recognized as a distinct patient group. As a result, AYA cancer patients often fall through the cracks of the traditional health care system and supportive care services. AYA cancer care is characterized by a distinct biology of cancers occurring at this age, differences in treatment response from those of other age groups, and the presence of key developmental milestones. Examples of these developmental milestones include completing education, finding first or pursuing employment, and starting a family [26]. Several studies have reported higher levels of distress and worse quality of life in AYA cancer patients compared to healthy matched peers or older adult cancer patients [27-29]. Despite the fact that overall survival for AYAs continues to lag behind that of children or older adults [30], advances in early detection and improvements in cancer treatments have resulted in an overall 5-year survival rate exceeding 80% [31]. With the expected further gains in overall survival of AYA cancer, persistent disease- and treatment-related symptoms that may compromise quality of life warrant early and adequate attention. In 2009, the Department of Medical Oncology at Radboudumc launched the first AYA outpatient clinic in the Netherlands in collaboration with the Department of Medical Psychology. The multidisciplinary team at the AYA clinic is available to all young adults who have (or had) cancer, regardless of their treatment status, type and intent of treatment. One of the issues experienced by young adults with cancer consulting the AYA outpatient clinic is CRF. It is believed that the impact of CRF might be even more pronounced
for AYA cancer patients compared to adult patients because it can interrupt with several developmental milestones. The prevalence, impact on quality of life, and associated factors of severe fatigue in patients with a diagnosis of cancer during young adulthood will be studied in the first part of this thesis.

Gastrointestinal stromal tumors
Gastrointestinal stromal tumors (GISTs) represent an extremely rare solid tumor with an estimated incidence rate of 250 to 300 cases per year in the Netherlands. Following the introduction of imatinib in 2001, a targeted therapy initially designed to treat chronic myeloid leukemia [32, 33], the perspective of metastatic GIST patients has changed significantly. Based on SEER data, cancer-specific survival of metastatic GIST increased from 15.0% (95% CI: 5.3 to 42.6%) in 1998 to 61.9% (95% CI: 51.4 to 74.5%) in 2008 (all P Trend < 0.05) [34]. Imatinib is taken orally on a daily basis and is generally well tolerated in comparison with traditional chemotherapy. However, fatigue is the most common, important and often complained of side effect experienced with the use of this drug and other tyrosine kinase inhibitors (TKIs). With the dramatically improved survival of patients with GISTs, management of TKI-related side effects as well as the impact of side effects on quality of life necessitates more attention. In the first part of this thesis, the prevalence, impact and associated factors of severe fatigue in a real-life and heterogeneous sample of GIST patients during and after TKI treatment will be studied.

Chronic myeloid leukemia
Chronic myeloid leukemia (CML) is a type of cancer that starts in certain blood-forming cells of the bone marrow. Every year, about 500 patients are diagnosed with CML in the Netherlands. It is a fairly slow growing leukemia, but it can change into a fast-growing acute leukemia that is hard to treat. A stem cell transplantation including high-dose chemotherapy and radiotherapy is the only potential cure for CML. However, with the introduction of imatinib and other TKIs it is now often possible to control CML for many years in such a way that the life expectancy of patients with CML approaches the life expectancy of the general population today [35]. With this improved survival and the need to continue lifelong treatment it is important to manage the side effects of these lifesaving drugs. Research demonstrated that chronic fatigue is the most important factor limiting quality of life in imatinib-treated CML patients [36]. Although cognitive-behavioural interventions are recommended to treat fatigue in cancer survivors in guidelines issued by the American Society of Clinical Oncology [37], efficacy of these interventions has not been examined in patients continuing lifelong treatment, such as patients with CML. CBT for CRF has been developed for and tested in disease-free cancer survivors that completed cancer treatment and where only perpetuating factors play a role. In CML patients who are chronically treated with TKIs, although stable with good prognosis, both precipitating
and perpetuating factors will contribute to perceived fatigue. Management of fatigue in patients receiving chronic treatment with TKIs to control their disease might require a slightly different approach or at least some tailoring to their specific situation and needs. The possibility to adapt an existing evidence-based CBT for CRF in disease-free cancer survivors [13] for application in patients with CML experiencing CRF as a lifesaving drug’s side effect was investigated in the first part of this thesis.

PART II: FATIGUE IN PATIENTS WITH INCURABLE DISEASE

Patients with a diagnosis of advanced or metastatic cancer are often overlooked and underrepresented in the area of CRF and the broader psychosocial oncology discussion. Yet, their experiences are commonly different from those with early-stage disease as they are, despite advances in treatment, diagnosed with a disease that remains essentially incurable. Advances in cancer treatment mean that patients with incurable cancer are living longer with a disease that can be controlled for months or even years. These patients must live with the prospects of inevitable progressive loss of condition, development of symptomatic disease and in the very end entering the terminal stage before death. This changes the outlook on life, as patients often point out themselves, it is not only the quantity but also the quality that is important. Consequently, next to prolonging patients’ lives, treatment of incurable cancer is also aimed at maintaining as high a quality of life for as long as possible and managing physical and psychological symptoms [38]. The second part of this thesis is concerned with studying CRF in incurable cancer patients. It involves a study on dyadic agreement between patients and informal or family caregivers on patients’ fatigue severity, the examination of effects of psychosocial interventions for severe fatigue in incurable cancer patients, followed by the development of a study protocol for an ongoing three-armed RCT along with considering the barriers and challenges associated with running this trial, including professional gatekeeping.

Fatigue during cancer treatment with palliative intent

CRF is frequently reported as one of the symptoms that significantly compromises quality of life in patients with incurable cancer. CRF prevents participation in preferred activities, hinders activities of daily living, and is often associated with emotional disturbances. As such, CRF affects not only patients but also their informal or family caregivers [39, 40]. It is generally agreed that patients are the best raters of their fatigue severity. However, it is also important to understand caregivers’ perceptions of patients’ fatigue severity during cancer treatment with palliative intent. Caregivers’ perceptions drive responses to patients’ fatigue, which in turn can have an impact on patients. In addition, since caregivers are increasingly involved in the care for patients with incurable cancer and the monitoring and management of treatment-
related symptoms, it is important to know whether they can give a meaningful additional rating of patients’ fatigue severity. The accuracy of caregiver ratings and the agreement over time along with predictors for agreement are examined in the second part of this thesis.

**Approaches for the management of CRF**

Given the profound impact of CRF on patients’ quality of life, it is surprising to note that, at present, there are no evidence-based interventions for CRF available for patients with incurable disease. Many factors are likely to contribute to CRF in patients with incurable cancer. CRF may result from the underlying disease or from secondary factors such as anemia, infection, malnutrition or dehydration, loss of muscle mass, pain, sleep disturbances, and treatment-related side effects. Furthermore, emotional distress including anxiety and depression, and cognitive or behavioural factors such as inappropriate coping or a low level of physical activity can also add to CRF [20, 21]. Management of CRF should first focus on identifying treatable somatic causes. However, clinical experience with fatigued patients indicates that a treatable somatic cause cannot always be found. Based on findings from previous studies in other cancer populations, two non-pharmacological approaches for CRF seem promising in the management of CRF in incurable cancer patients. The first approach is concerned with optimising levels of physical activity through exercise therapy, which can be helpful in reducing CRF by improving physical capacity [41]. The second approach comprises psychosocial interventions for CRF, aimed at changing fatigue-related thoughts, emotions and behaviours [18]. The second part of this thesis includes a systematic review and meta-analysis of completed psychosocial interventional studies for the management of CRF in the subgroup of participants receiving treatment for incurable cancer.

**The TIRED study: a randomised controlled trial**

The efficacy of exercise or psychosocial interventions in reducing fatigue has not yet been examined in a large and homogeneous sample of patients with incurable cancer receiving treatment with palliative intent. Moreover, the role of the assumed mechanisms of change for these interventions, that is, a change in physical condition versus a change in fatigue-related cognitions, remains to be determined. We will describe the development of a study protocol for a three-armed RCT aimed to address CRF in patients receiving treatment for incurable cancer by either exercise therapy or CBT compared to usual care (TIRED study). Following previous experiences with CRF intervention research, we aimed to select only those patients most in need for a fatigue intervention for the TIRED study [18]. Therefore, potential participants were screened on the presence of severe fatigue by means of administering a multidimensional fatigue questionnaire with a validated cut-off for severe fatigue. Patient identification and recruitment for the TIRED study started in January 2013 and proved
to be extremely challenging from the beginning. One well-known and persistent problem in palliative care research is gatekeeping by healthcare professionals, which can be described as professionals preventing potentially eligible patients from entering a supportive care trial as a participant. Gatekeeping by professionals was also observed in the TIRED study and jeopardized successful patient identification and recruitment. We will investigate whether gatekeeping is justified from a patient’s point of view. After a recruitment period of more than four years, we reached only 80% of our required sample size and thus enrolment of participants for the TIRED study is still ongoing. Results on the efficacy of the interventions and potential mechanisms of change are not expected until 2018 and will, therefore, be reported elsewhere. Lessons learned from conducting the TIRED study will be shared. These valuable insights will hopefully serve other investigators interested in performing intervention research for this important but complex patient population.

AIMS OF THE THESIS

The overall purpose of this thesis is to further develop existing knowledge on CRF and its management in understudied cancer populations in psychosocial oncology. The studies reported in this thesis are aimed to gain insight into the prevalence, impact and associated factors of CRF in patients with a rare cancer diagnosis, to test whether existing evidence-based interventions for CRF can be adapted for new target populations, to determine whether informal caregivers are able to provide an accurate additional rating of patients’ fatigue severity during cancer treatment with palliative intent, and to examine the current evidence on the effects of psychosocial interventions for fatigue in patients with incurable cancer, as well as to describe the development and conduct of an ongoing large-scale interventional study examining the effects of an exercise and psychosocial intervention for severe fatigue in patients with incurable cancer.

OUTLINE OF THE THESIS

This thesis consists of ten chapters divided into two parts. The first part of this thesis is focused on fatigue in patients primarily characterized by a diagnosis of a rare cancer or with a cancer diagnosis at an uncommon age. The cross-sectional study described in Chapter 2 investigated the prevalence of severe CRF in patients diagnosed with cancer during adolescence and young adulthood compared with matched population-based controls. This chapter also reports on the impact of severe fatigue on the quality of life of AYA cancer patients. In addition, correlates of fatigue severity were studied. Chapter 3 reports on the prevalence and impact of severe fatigue in patients
with GIST, a rare type of sarcoma. The introduction of TKIs has revolutionized the treatment of GIST. However, the use of TKIs is limited by the occurrence of different side effects, such as fatigue. In this chapter, several psychosocial, disease- and treatment-related factors were studied as potential correlates of fatigue severity in GIST patients during and after TKI treatment. Based on previous studies performed at the ECCF, Chapter 4 describes the adaptation of an evidence-based intervention for severe fatigue in disease-free cancer patients to address fatigue in CML patients receiving long-term TKI therapy. In this study, it was investigated whether the existing intervention could be successfully adapted for application in a new target population. The second part of this thesis is focused on fatigue in patients all diagnosed with incurable cancer. The longitudinal study presented in Chapter 5 evaluates agreement between incurable cancer patients and their informal caregivers about patients’ fatigue severity during cancer treatment with palliative intent. In addition, agreement over time and predictors of agreement are examined. To get a better understanding of the effects of psychosocial interventions on fatigue in patients with incurable cancer, Chapter 6 includes a systematic review and meta-analysis of available data from completed trials with patients during cancer treatment with palliative intent. Building on an established patient need and the results of Chapter 6, the design and rationale of a still ongoing RCT focused on addressing fatigue in incurable cancer patients (TIRED study) is described in Chapter 7. Chapter 8 reports on whether gatekeeping by health care professionals, a major barrier in patient recruitment for palliative supportive care trials, is justified. To facilitate future RCTs testing a supportive care intervention in advanced cancer patients, Chapter 9 captures valuable lessons learned from patient identification and recruitment for the TIRED study and shares strategies to overcome barriers and challenges that were encountered. Finally, Chapter 10 entails a summary and discussion in which practical implications of the findings presented in this thesis are discussed and recommendations for future research are formulated.
REFERENCES


PART I

FATIGUE IN PATIENTS WITH RARE CANCER
CHAPTER 2

PREVALENCE AND IMPACT OF SEVERE FATIGUE IN ADOLESCENT AND YOUNG ADULT CANCER PATIENTS IN COMPARISON WITH POPULATION-BASED CONTROLS

Hanneke Poort, Suzanne Kaal, Hans Knoop, Rosemarie Jansen, Judith Prins, Eveliene Manten-Horst, Petra Servaes, Olga Husson, Winette van der Graaf

Supportive Care in Cancer, 2017; Epub ahead of print
ABSTRACT

Background
The current study determined the prevalence of severe fatigue in Adolescent and Young Adult (AYA) cancer patients (aged 18-35 years at diagnosis) consulting a multidisciplinary AYA team in comparison with gender- and age-matched population-based controls. In addition, impact of severe fatigue on quality of life and related factors of fatigue severity were examined.

Methods
AYAs with cancer (n=83) completed questionnaires including the Checklist Individual Strength (CIS-fatigue), Quality of Life (QoL)-Cancer Survivor, Hospital Anxiety and Depression Scale (reflecting psychological distress), and the Cancer Worry Scale (reflecting fear of cancer recurrence or progression).

Results
The vast majority of participants had been treated with chemotherapy (87%) and had no active treatment at the time of participation (73.5%). Prevalence of severe fatigue (CIS-fatigue score ≥ 35) in AYAs with cancer (48%, n=40/83) was significantly higher in comparison with matched population-based controls (20%, n=49/249; p < .001). Severely fatigued AYAs with cancer reported lower QoL compared to non-severely fatigued AYAs with cancer (p’s < .05). Female gender, being unemployed, higher disease stage (III-IV) at diagnosis, receiving active treatment at the time of participation, being treated with palliative intent, having had radiotherapy, higher fear of recurrence or progression, and higher psychological distress were significantly correlated with fatigue severity (p’s < .05).

Conclusion
Severe fatigue based on a validated cut-off score was highly prevalent in this group of AYAs with cancer. QoL is significantly affected by severe fatigue, stressing the importance of detection and management of this symptom in those patients affected by a life-changing diagnosis of cancer in late adolescence or young adulthood.
INTRODUCTION

Compared to adults, a diagnosis of cancer in adolescents and young adults (AYAs) between the ages of 18 and 35 years is rare. Advances in early detection and improvements in cancer treatments have resulted in an overall 5-year survival rate exceeding 80% in AYAs [1]. While AYAs with cancer face challenges similar to adult cancer patients, those in the heart of their youth experience unique cancer-related challenges in addition to usual age-related developmental tasks. The combination of achieving normal developmental milestones and simultaneously coping with a life-changing diagnosis of cancer frequently leads to psychosocial issues among AYAs with cancer [2]. Several studies have documented higher levels of distress and lower quality of life (QoL) in AYAs with cancer in comparison with healthy matched peers or adult cancer patients [3-5]. Moreover, treatment-related symptoms (e.g. pain and fatigue) and late effects (e.g. second cancers and cardiovascular disease) can interfere with a healthy body image, establishing social relationships, or attaining levels of autonomy and independence. With the expected further gains in overall survival of AYA cancer, it is important to address persistent disease- and treatment-related symptoms that compromise several domains of QoL.

Cancer-related fatigue (CRF) is one of the most common and distressing symptoms reported by adult and childhood cancer patients both during and after cancer treatment [6, 7]. The most commonly used definition for CRF is formulated by the National Comprehensive Cancer Network (NCCN) and defines CRF as “a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity that interferes with usual functioning” [8]. The vast majority of studies on the prevalence and severity of CRF have been conducted in adult or childhood cancer patients and only a few studies evaluated fatigue severity in AYAs with cancer. Moreover, the limited AYA-specific studies did not attempt to report on clinically relevant levels of fatigue by using a validated cut-off for severe fatigue [4, 9].

Knowledge on the prevalence of severe fatigue in AYAs with cancer is important, as we know from studies in adult cancer patients that severe fatigue is associated with more functional impairments, lower QoL, and more distress [6, 10]. For AYAs with cancer, the impact of severe fatigue might be even more pronounced because it can interrupt developmental milestones such as completing education, finding first or pursuing employment, beginning a romantic relationship, or starting a family. Understanding factors related to severe fatigue among AYAs with cancer will help health care providers identify who is more likely to experience this symptom. In addition, it will help researchers to determine potential factors that could be addressed in interventions targeting fatigue.
The present study determined the prevalence of clinically relevant levels of fatigue in AYAs with cancer using a validated cut-off for severe fatigue and compared the proportion of severely fatigued cases with the proportion of severely fatigued cases in a sample of gender- and age-matched population-based controls. In addition, the impact of severe fatigue on QoL and potential sociodemographic, treatment-related, and psychological correlates of fatigue severity was explored. A cross-sectional approach was used for this study to gather descriptive information about the presence of clinically relevant levels of fatigue among AYAs with cancer.

MATERIALS AND METHODS

Patients
Patients aged 18-35 years at cancer diagnosis and who had been seen by at least one of the members of the AYA team of the Radboud university medical center, Nijmegen, The Netherlands, were invited to participate in this study. The AYA team is a dedicated multidisciplinary team including a medical oncologist, clinical nurse specialist, medical psychologist, and social worker. Patients consulting the AYA team receive regular medical care from their own treating specialist (oncologist, surgeon, haematologist, dermatologist, urologist, gynaecologist, etc.) and visit the AYA team for age-specific questions and care needs. In general, patients visiting the AYA team represent a group of patients with higher disease severity, diagnosed with relatively advanced stage of disease and undergoing intensive treatments, and reporting more problems with coping. The AYA team does not often see patients with low stage disease treated solely by surgery, such as in the case of thin melanomas.

To depict the real-life heterogeneous sample of AYAs with cancer visiting the AYA team, AYAs with cancer were included in this first study on the prevalence of severe fatigue regardless of treatment status (during or after treatment), type of treatment (surgery, chemotherapy, radiotherapy, immunotherapy, targeted therapy, hormonal therapy or combination), or the number of AYA team visits (some patients only had one introduction talk with one of the members of the team and did not receive specific care thereafter). Inclusion commenced January 2012 and ended March 2016.

Population-based controls
Population-based controls were derived from a cohort of panel members surveyed by CentERdata, a research institute at Tilburg University collecting data from a sample of more than 2000 Dutch households (http://www.centerdata.nl/en/). This CentERpanel represents the adult Dutch-speaking population with respect to demographic characteristics. Population-based controls provided self-reported data on age and gender and completed a multi-dimensional fatigue questionnaire (Checklist Individual
Strength, see measures). They had no sickness absence in the workplace (0 days) in the month prior to filling in the questionnaires. Further information on the presence of physical or mental health conditions in population-based controls was not available.

**Procedure**

Potential study participants were recruited via letters describing the study and inviting patients to participate in the study. Patients willing to participate had to actively opt-in to the study by providing written informed consent by email to a member of the AYA team. Participants were then sent a single set of questionnaires by email that could be completed online. The study was deemed exempt from full review and approval by a research ethics committee (CMO Regio Arnhem-Nijmegen, 2016-2872).

**Measures**

AYAs with cancer completed a self-report questionnaire on sociodemographic data (i.e., age, gender, partner status, having children, education level, and employment status). A member of the AYA team (SK) extracted clinical data (i.e., cancer diagnosis, disease stage at diagnosis, time since initial cancer diagnosis, type(s) of treatment(s) received, duration of cancer treatment, treatment status at participation, and time since completion of cancer treatment) from patients’ medical records. AYAs with cancer completed the following questionnaires, including a multi-dimensional fatigue questionnaire:

*Checklist Individual Strength, subscale fatigue severity (CIS-fatigue).* The subscale fatigue severity of the CIS consists of eight items scored on a 7-point Likert scale. Total CIS-fatigue scores can range from 8 to 56, with scores greater than 34 indicating clinically relevant levels of fatigue [11]. The CIS-fatigue has been used in previous studies examining severe fatigue in cancer patients during and after cancer treatment [12-14]. A cut-off was used to group AYAs with cancer into two groups to indicate severely fatigued (≥ 35) and non-severely fatigued patients (< 35).

*Quality of Life-Cancer Survivor (QoL-CS).* The QoL-CS consists of 41 items scored on a 10-point Likert scale [15]. The impact of cancer diagnosis and treatment is assessed with four subscales, i.e., physical, social, psychological, and spiritual wellbeing. In addition to the four subscale scores, the total QoL score reflecting the average across all items was used in this study. Higher scores indicated better QoL for all subscales.

*Hospital Anxiety and Depression Scale (HADS).* The HADS consists of 14 items scored on a 4-point Likert scale [16]. The summed total HADS scores range from 0 to 42, and were used to reflect psychological distress in our sample of AYAs with cancer [17]. Higher total scores indicate more psychological distress.
Cancer Worry Scale (CWS). The CWS consists of eight items regarding concerns about cancer recurrence or progression of cancer. Items are scored on a 4-point Likert scale ranging from ‘never’ to ‘almost always’ [18]. Total CWS scores range from 8 to 32, and can be used to assess cancer worrying. Higher total scores indicate more fear of cancer recurrence or progression. Patients with a recent recurrence ($n=5$) or receiving treatment with palliative intent ($n=7$) did not complete the CWS because the item wording of this measure was irrelevant to them.

Statistical Analyses
To compare mean fatigue severity and the prevalence of severe fatigue in AYAs with cancer with population-based controls derived form the sample of CentERdata ($n=1923$), AYAs with cancer were matched on gender and age (within a range of 0 to 5 years) with 249 population-based controls. Given the relatively low proportion of CentERpanel members within the age range of our study sample, the highest possible ratio for matching AYAs with cancer to controls was 1:3. Precision matching was performed with STATA/SE. All other analyses were performed using SPSS Statistics (version 22.0). Descriptive statistics and frequencies concerning socio-demographic and clinical data were calculated. An independent samples $t$-test was used to compare fatigue severity scores between AYAs with cancer and matched population-based controls. We used a Chi-square test to compare the proportion of severely fatigued cases in AYAs with cancer and matched population-based controls. Pearson and Point-Biserial correlations were calculated to examine associations between continuous variables or continuous and dichotomous variables, respectively. The significance level was set at .05. We did not adjust for multiple testing.

RESULTS
In total, 309 letters requesting participation in the study were sent to AYAs with cancer visiting one of the members of the AYA team. The total sample of 89 participants comprised 57% of those who opted-in to the study ($n=55$) and 29% of all those solicited by mail ($n=309$). Six participants were excluded, four since they were diagnosed with cancer under the age of 18 years and two because they were aged above 35 years at diagnosis. Table 1 displays sociodemographic, disease and treatment-related characteristics of the final sample of 83 AYAs with cancer stratified by the presence of severe fatigue. Mean age at cancer diagnosis for the total sample was 27.3 years (SD 4.4) and mean time since cancer diagnosis was 2.1 years (SD 2.6). The most common diagnosis was testicular cancer (34%) followed by sarcoma (19%). Disease stage at diagnosis was known and applicable in 67 participants. Of those, 36 (54%) were diagnosed with early-stage disease (stages I-II) and 31 (46%) with late-stage disease (stages III-IV). The majority of participants
had undergone surgery (n=70, 84%) and chemotherapy (n=72, 87%), but were not on active cancer treatment at the time of study participation (n=61, 73.5%). Mean duration of cancer treatment was 15.8 months (SD 20.6). For the subset of 61 patients not on active cancer treatment at the time of study participation, mean duration since completion of treatment was 17.5 months (SD 30.6).

Table 1. Characteristics of the study sample stratified by fatigue severity

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total sample (n=83)</th>
<th>Non-severely fatigued patients (n=43)</th>
<th>Severely fatigued patients (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at cancer diagnosis,</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (SD)</td>
<td>27.3 (4.4)</td>
<td>26.5 (4.6)</td>
<td>28.0 (4.1)</td>
</tr>
<tr>
<td>18-25 years</td>
<td>30 (36%)</td>
<td>18 (42%)</td>
<td>12 (30%)</td>
</tr>
<tr>
<td>26-35 years</td>
<td>53 (64%)</td>
<td>25 (58%)</td>
<td>28 (70%)</td>
</tr>
<tr>
<td><strong>Age at participation,</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (SD)</td>
<td>29.4 (4.7)</td>
<td>28.7 (5.0)</td>
<td>30.2 (4.4)</td>
</tr>
<tr>
<td>18-25 years</td>
<td>19 (23%)</td>
<td>13 (30%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>26-35 years</td>
<td>58 (70%)</td>
<td>27 (63%)</td>
<td>31 (77.5%)</td>
</tr>
<tr>
<td>&gt; 35 years</td>
<td>6 (7%)</td>
<td>3 (7%)</td>
<td>3 (7.5%)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>43 (52%)</td>
<td>30 (70%)</td>
<td>13 (32.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>40 (48%)</td>
<td>13 (30%)</td>
<td>27 (67.5%)</td>
</tr>
<tr>
<td><strong>Partner a</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>58 (70%)</td>
<td>32 (74%)</td>
<td>26 (67%)</td>
</tr>
<tr>
<td>No</td>
<td>24 (29%)</td>
<td>11 (26%)</td>
<td>13 (33%)</td>
</tr>
<tr>
<td><strong>Children a</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27 (33%)</td>
<td>30 (70%)</td>
<td>25 (64%)</td>
</tr>
<tr>
<td>No</td>
<td>55 (66%)</td>
<td>13 (30%)</td>
<td>14 (36%)</td>
</tr>
<tr>
<td><strong>Highest completed education a</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>36 (43%)</td>
<td>18 (42%)</td>
<td>18 (46%)</td>
</tr>
<tr>
<td>High</td>
<td>44 (53%)</td>
<td>25 (58%)</td>
<td>19 (49%)</td>
</tr>
<tr>
<td><strong>Employed or studying a</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>53 (64%)</td>
<td>37 (86%)</td>
<td>16 (40%)</td>
</tr>
<tr>
<td>No</td>
<td>26 (31%)</td>
<td>4 (9%)</td>
<td>22 (55%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (4%)</td>
<td>2 (5%)</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td><strong>Cancer diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testicular cancer</td>
<td>28 (34%)</td>
<td>22 (51%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>16 (19%)</td>
<td>5 (12%)</td>
<td>11 (27.5%)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>10 (12%)</td>
<td>4 (9%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Haematological malignancy</td>
<td>10 (12%)</td>
<td>2 (5%)</td>
<td>8 (20%)</td>
</tr>
<tr>
<td>Gynaecological cancer</td>
<td>9 (11%)</td>
<td>5 (12%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3 (4%)</td>
<td>2 (5%)</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>Other b</td>
<td>7 (8%)</td>
<td>3 (7%)</td>
<td>4 (10%)</td>
</tr>
</tbody>
</table>

a Information was not available for one AYA with cancer. b Including: glioma (n=1) sigmoid carcinoma (n=1), oropharyngeal cancer (n=1), neuroendocrine tumor (n=1), lung cancer (n=1), salivary gland cancer (n=1), and adrenal cancer (n=1).
Table 1. Characteristics of the study sample stratified by fatigue severity (continued)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total sample (n=83)</th>
<th>Non-severely fatigued patients (n=43)</th>
<th>Severely fatigued patients (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer stage at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not applicable</td>
<td>9 (11%)</td>
<td>3 (7%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Stage I</td>
<td>11 (13%)</td>
<td>6 (14%)</td>
<td>5 (12.5%)</td>
</tr>
<tr>
<td>Stage II</td>
<td>25 (30%)</td>
<td>18 (42%)</td>
<td>7 (17.5%)</td>
</tr>
<tr>
<td>Stage III</td>
<td>13 (16%)</td>
<td>3 (7%)</td>
<td>10 (25%)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>18 (22%)</td>
<td>11 (26%)</td>
<td>7 (17.5%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7 (8%)</td>
<td>2 (5%)</td>
<td>5 (12.5%)</td>
</tr>
<tr>
<td>Time since cancer diagnosis, mean (SD) in years</td>
<td>2.1 (2.6)</td>
<td>2.0 (1.8)</td>
<td>2.2 (3.3)</td>
</tr>
<tr>
<td>Lifetime cancer treatment c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>70 (84%)</td>
<td>38 (88%)</td>
<td>32 (80%)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>72 (87%)</td>
<td>38 (88%)</td>
<td>34 (85%)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>24 (29%)</td>
<td>10 (23%)</td>
<td>14 (35%)</td>
</tr>
<tr>
<td>Immuno- or targeted therapy</td>
<td>13 (16%)</td>
<td>5 (12%)</td>
<td>8 (20%)</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>7 (8%)</td>
<td>4 (9%)</td>
<td>3 (7.5%)</td>
</tr>
<tr>
<td>Duration of cancer treatment, mean (SD) in months</td>
<td>15.8 (20.6)</td>
<td>15.0 (22.1)</td>
<td>16.7 (19.2)</td>
</tr>
<tr>
<td>Intent of cancer treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curative</td>
<td>71 (85.5%)</td>
<td>40 (93%)</td>
<td>31 (77.5%)</td>
</tr>
<tr>
<td>Palliative</td>
<td>12 (14.5%)</td>
<td>3 (7%)</td>
<td>9 (22.5%)</td>
</tr>
<tr>
<td>Treatment status at participation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No active treatment</td>
<td>61 (73.5%)</td>
<td>36 (83.7%)</td>
<td>25 (62.5%)</td>
</tr>
<tr>
<td>Active treatment</td>
<td>22 (26.5%)</td>
<td>7 (16.3%)</td>
<td>15 (37.5%)</td>
</tr>
</tbody>
</table>

c Multiple answers possible.

Prevalence of Severe Fatigue and Impact on Quality of Life
AYAs with cancer reported a significantly higher fatigue severity score than matched population-based controls (31.5, SD 11.8 versus 24.9, SD 10.5, respectively, p < .001). The prevalence of severe fatigue in AYAs with cancer was significantly higher in comparison with matched population-based controls (48%, n=40/83 versus 20%, n=49/249, respectively, p < .001). Severely fatigued AYAs with cancer reported significantly lower scores on all four QoL subscales (i.e., physical, social, psychological, and spiritual well-being) and on total QoL, compared to their non-severely fatigued counterparts (p’s < .05, see Table 2).
Fatigue in AYAs with cancer

Table 2. Impact of Severe Fatigue on Quality of Life of AYAs with cancer

<table>
<thead>
<tr>
<th>QoL-CS</th>
<th>Non-severely fatigued patients (n=43)</th>
<th>Severely fatigued patients (n=40)</th>
<th>Mean difference</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical well-being</td>
<td>8.28 (± 1.21)</td>
<td>6.57 (± 1.49)</td>
<td>-1.71</td>
<td>.000**</td>
</tr>
<tr>
<td>Social well-being</td>
<td>5.41 (± 1.33)</td>
<td>4.81 (± 1.30)</td>
<td>-0.60</td>
<td>.042*</td>
</tr>
<tr>
<td>Psychological well-being</td>
<td>6.27 (± 1.29)</td>
<td>4.90 (± 1.59)</td>
<td>-1.37</td>
<td>.000**</td>
</tr>
<tr>
<td>Spiritual well-being</td>
<td>4.21 (± 1.16)</td>
<td>3.29 (± 1.36)</td>
<td>-0.92</td>
<td>.001**</td>
</tr>
<tr>
<td>Total QoL</td>
<td>6.12 (± 0.82)</td>
<td>4.95 (± 1.13)</td>
<td>-1.17</td>
<td>.000**</td>
</tr>
</tbody>
</table>

*Mean difference is significant at the 0.05 level. **Mean difference is significant at the 0.01 level.

Table 3. Correlates of Fatigue Severity in AYAs with cancer

<table>
<thead>
<tr>
<th>Correlates</th>
<th>Correlation coefficients</th>
<th>N</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographic variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at cancer diagnosis</td>
<td>.194</td>
<td>83</td>
<td>.079</td>
</tr>
<tr>
<td>Age at participation</td>
<td>.185</td>
<td>83</td>
<td>.093</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>.336</td>
<td>83</td>
<td>.002**</td>
</tr>
<tr>
<td>Partner status (yes/no)</td>
<td>.118</td>
<td>82</td>
<td>.291</td>
</tr>
<tr>
<td>Children (yes/no)</td>
<td>-.122</td>
<td>82</td>
<td>.273</td>
</tr>
<tr>
<td>Employed or studying (yes/no)</td>
<td>.394</td>
<td>79</td>
<td>.000**</td>
</tr>
<tr>
<td><strong>Disease and treatment-related variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since cancer diagnosis</td>
<td>.073</td>
<td>83</td>
<td>.513</td>
</tr>
<tr>
<td>Cancer stage at diagnosis (early/late)(^a)</td>
<td>.322</td>
<td>67</td>
<td>.008*</td>
</tr>
<tr>
<td>Duration of cancer treatment</td>
<td>.087</td>
<td>81</td>
<td>.439</td>
</tr>
<tr>
<td>Cancer treatment at participation (yes/no)</td>
<td>-.227</td>
<td>83</td>
<td>.039*</td>
</tr>
<tr>
<td>Time since completion of cancer treatment</td>
<td>.060</td>
<td>61</td>
<td>.646</td>
</tr>
<tr>
<td>Intent of cancer treatment (curative/palliative)</td>
<td>.270</td>
<td>83</td>
<td>.013*</td>
</tr>
<tr>
<td>Surgery (yes/no)</td>
<td>.178</td>
<td>83</td>
<td>.108</td>
</tr>
<tr>
<td>Chemotherapy (yes/no)</td>
<td>.115</td>
<td>83</td>
<td>.302</td>
</tr>
<tr>
<td>Radiotherapy (yes/no)</td>
<td>-.242</td>
<td>83</td>
<td>.028*</td>
</tr>
<tr>
<td>Immuno- or targeted therapy (yes/no)</td>
<td>-.107</td>
<td>83</td>
<td>.336</td>
</tr>
<tr>
<td>Hormone therapy (yes/no)</td>
<td>.064</td>
<td>83</td>
<td>.563</td>
</tr>
<tr>
<td><strong>Psychological variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological distress (HADS total)</td>
<td>.553</td>
<td>83</td>
<td>.000**</td>
</tr>
<tr>
<td>Fear of recurrence or progression (CWS total)(^b)</td>
<td>.340</td>
<td>71</td>
<td>.004**</td>
</tr>
</tbody>
</table>

*Correlation is significant at the 0.05 level. **Correlation is significant at the 0.01 level. \(^a\) Cancer stage was unknown for n=7 AYAs with cancer and not applicable for n=9 AYAs with cancer. \(^b\) CWS was not administered to n=12 AYAs with cancer, because they either had a recurrence (n=5) or received treatment with palliative intent (n=7).
Sociodemographic, Treatment-Related, and Psychosocial Correlates of Fatigue Severity

Correlations are listed in Table 3. Higher psychological distress was strongly correlated to fatigue severity \((R = .55; p < .001)\). Female gender, being unemployed (not having a job, sick leave or disablement insurance act), higher disease stage (III-IV) at diagnosis, and higher fear of recurrence or progression were moderate correlates \((R's 0.30 to 0.50; p's < .01)\). In addition, receiving active treatment at the time of study participation, palliative intent of treatment and having had radiotherapy were weakly associated with fatigue severity \((R's 0.10 to 0.30; p's < .05)\). No significant associations were observed between fatigue severity and the other sociodemographic, disease- and treatment related variables (see Table 3; \(p's > .05)\).

DISCUSSION

In this study, severe fatigue affected almost half of the AYAs with cancer. The prevalence of severe fatigue in AYAs with cancer was more than twice as high in AYAs with cancer than in gender- and age-matched population-based controls (48% versus 20%). Severe fatigue as assessed with the CIS-fatigue is more prevalent amongst AYAs with cancer than adult disease-free breast cancer patients 3 years after diagnosis (38%) [19]. The prevalence amongst AYAs with cancer corresponds more closely with findings from a study performed in adult cancer patients during cancer treatment with palliative intent (47%) [13], which is remarkable given the major difference in prognosis between these two patient groups. In our sample, only a minority of the participants \((n=12, 14.5\%)\) were classified as being treated with palliative intent at the time of participation. Reasons for the high prevalence of severe fatigue in AYAs with cancer have not been studied. One might postulate that, in contrast to adult cancer patients, the higher prevalence of severe fatigue originates from the unique combination of being diagnosed and treated for cancer and the developmental milestones AYAs are confronted with during adolescence and young adulthood.

Alternatively, the higher prevalence of severe fatigue reported by participants in our study could be the result of selection bias. We recruited AYAs with cancer that consulted a multidisciplinary AYA team. The fact that patients consulted a specialized AYA team most likely indicates that these patients had additional disease and/or treatment-related questions or problems, although not all patients had a need for continued and specific care by the AYA team after the first consultation. The percentage of patients having had chemotherapy as part of AYA cancer treatment was high (87%). This further supports the likelihood of selection bias in our sample and might overestimate disease severity of the entire AYA cancer patient population.
Nonetheless, we can conclude that within the subset of AYAs with cancer consulting a multidisciplinary AYA team, the prevalence of severe fatigue is substantial.

Significant differences were found in physical, social, psychological, spiritual, and total QoL for severely fatigued AYAs with cancer in comparison with non-severely fatigued patients, which echoes previous studies reporting on the detrimental effects of severe fatigue in adult cancer patients [6, 10]. More psychological distress was a strong correlate of fatigue severity in the present study. In addition, more cancer worrying, female gender, and being unemployed were moderately related to fatigue severity. Geue et al. (2014) studied gender-specific differences in quality of life after AYA cancer and found lower QoL for women than men, including higher levels of fatigue [20]. The finding that more psychological distress and cancer worrying were associated with fatigue severity is in agreement with the impact of fatigue severity on QoL of AYAs with cancer in this study. However, given the cross-sectional design of our study we cannot draw conclusions on causality. This also limits interpreting the finding that being unemployed was linked to higher fatigue severity, although it may suggest that severely fatigued AYAs with cancer might not be able to find appropriate work. This emphasises the relevance of further research into this topic.

We only found weak or non-significant links between treatment-related variables and fatigue severity; receiving active treatment at the time of study participation, receiving treatment with palliative intent, and having had radiotherapy were significant but weakly related to fatigue severity. A moderate association was found between late-stage cancer at diagnosis and fatigue severity. In previous studies among adult cancer patients during and after treatment, fatigue appeared to be unrelated to disease-related variables, but the receipt of chemotherapy was associated with fatigue long after treatment [21]. A recently published review among breast cancer survivors after treatment also reported that survivors treated with chemotherapy were at higher risk for developing severe fatigue, as were those survivors with a higher disease stage at diagnosis [22]. As mentioned before, a noteworthy proportion of participants (87%) in our sample had been treated with chemotherapy.

The present study has several limitations. The sample size of our study was relatively small and the low participation rate increases the probability of bias by non-response. Unfortunately, small sample sizes are also seen in other studies in which patients of AYA age are asked to participate [23, 24]. Recruitment for our study took place over a period of 4 years. Additional efforts to increase data collection, such as multiple mailings of questionnaires or follow-up phone calls, were only made in the latter part of the study. Our response rate might have been higher when these efforts were made throughout the entire duration of the study. However, in the AYA HOPE study fewer than half of the eligible AYAs with cancer responded to questionnaires despite
extensive efforts such as multiple mailings, phone calls, and financial incentives [25]. One way to overcome the low response rate in AYA cancer research might be the use of in-person contact and patient-preferred paper-pencil rather than online surveys as recently suggested by Rosenberg et al. [26]. Given the low incidence of cancer in AYAs between the ages of 18 to 35 years, recruitment from multiple institutions in an (inter)national AYA network could also aid the collection of larger samples. This would also increase the ability to generalize findings, which is limited in our study since we recruited patients at a single university medical center. While a broad range of potential correlates of fatigue severity was studied, we cannot rule out the involvement of other potentially relevant factors that have not been examined in this study. For example, sleep problems are strongly correlated with higher levels of fatigue in patients with cancer [27]. In addition, a low level of physical activity and pain are also correlated with cancer-related fatigue [28]. There is evidence that the effect of sleep problems on fatigue is mediated by pain [29]. Unfortunately, we did not include validated instruments to assess sleep problems, physical activity, and pain as potential correlates of fatigue severity in our sample, which is a significant limitation of the study. Notwithstanding these limitations, the present study is the first to apply a clinically relevant cut-off for severe fatigue in AYAs with cancer aged between 18 and 35 years at diagnosis.

In conclusion, given the high prevalence and significant impact of severe fatigue on quality of life of AYAs with cancer, health care providers should pay careful attention to this symptom. In particular, female AYAs with cancer, those with more advanced disease at diagnosis, higher levels of psychological distress, and more cancer worrying seem to experience higher levels of fatigue. The longer-term survivorship rates of AYA cancer illustrate the potential longevity of AYAs with cancer. It is therefore important to investigate the course and persistence of severe fatigue in AYAs with cancer in longitudinal, population-based studies. Such studies would also aid the development of age-specific interventions addressing persistent cancer-related fatigue in AYAs with cancer to enable full participation in society throughout survivorship. Although evidence-based interventions for the management of cancer-related fatigue in adult cancer survivors are available and recommended within guidelines issued by the American Society for Clinical Oncology [30], these interventions have not been tested extensively in AYAs with cancer. Researchers should investigate whether these interventions can also be successfully applied to alleviate persistent cancer-related fatigue, improve QoL, and facilitate participation in society for the understudied population of AYAs with cancer.
REFERENCES


Fatigue in AYAs with cancer
CHAPTER 3

PREVALENCE, IMPACT, AND CORRELATES OF SEVERE FATIGUE IN PATIENTS WITH GASTROINTESTINAL STROMAL TUMORS

Hanneke Poort, Winette van der Graaf, Ronald Tielen, Myrella Vlenterie, José Custers, Judith Prins, Stans Verhagen, Marieke Gielissen, Hans Knoop

ABSTRACT

Background
The introduction of the tyrosine kinase inhibitor (TKI) imatinib in the treatment of Gastro Intestinal Stromal Tumor (GIST) in 2000 was the start of a new era of targeted treatment. Since then the median survival of patients with GIST has substantially increased. Prolonged survival and chronic TKI use are associated with treatment-induced symptoms, such as fatigue, which can compromise quality of life (QoL). This study determined the prevalence of severe fatigue in GIST patients compared to matched healthy controls (MHCs), the impact of fatigue on daily life, and associations between fatigue and current TKI use.

Methods
119 patients treated with surgery and/or a TKI for GIST were asked to participate. Participants completed questionnaires including the Checklist Individual Strength (CIS-fatigue), SF36-item Health Survey, EORTC-QoL Questionnaire, Fatigue Catastrophizing Scale, Self-Efficacy Scale, and the Hospital Anxiety and Depression Scale.

Results
89 GIST patients (75%) completed questionnaires, 61 patients (69%) were on a TKI. Prevalence of severe fatigue measured with the CIS-fatigue was significantly higher in GIST patients (30%) than in 234 MHCs (15%). The prevalence of severe fatigue did not differ significantly between patients receiving treatment with curative (29%) or palliative intent (36%). Severely fatigued patients reported lower QoL and more impairment on all functional domains. TKI use, more psychological distress, and lower physical functioning were associated with fatigue.

Conclusion
Severe fatigue occurs in 30% of GIST patients and in 33% of GIST patients on a TKI. The fatigue is disabling and is not only associated with current TKI use, but also with psychological distress and physical functioning. GIST patients should be informed about these associated factors of fatigue that deserve appropriate management.
INTRODUCTION

Gastro-intestinal stromal tumors (GISTs) are the most frequent sarcomas of the gastrointestinal tract. It is a rare type of cancer, as all sarcomas represent about 1% of adult cancers. The curative treatment for localized GIST is radical surgical resection. However, GISTs are known for their recurrent nature and are regarded resistant to conventional chemotherapeutic agents and radiation therapy [1]. The introduction of the tyrosine kinase inhibitor (TKI) imatinib in 2000 and new TKIs in more recent years has changed the treatment of GIST profoundly [2]. Patients with locally advanced or metastatic GIST currently face an extended median overall survival from less than 1 year in the past [1] to over 5 years nowadays [3]. Due to this extended survival, aspects regarding the quality of life become more relevant.

Fatigue is one of the most frequently reported symptoms by cancer patients, especially during cancer treatment [4]. Although treatment with imatinib is generally well tolerated, almost all patients have at least one adverse event of any grade [5, 6]. Clinical trials investigating the tolerability and safety of imatinib most frequently use the National Cancer Institute-Common Terminology Criteria (NCI-CTC) to determine presence and severity of treatment-induced toxicities [7]. This clinician-assessed measure results in a classification of symptoms in grade I-II (mild-moderate) to grade III-IV (severe-disabling). While mild fatigue is a frequent toxicity of imatinib, severe or disabling fatigue is less often reported. However, it is known that the use of clinician-reported measures underestimates the occurrence and severity of symptoms [8]. Patient-reported outcomes are more sensitive and valid measures for assessing fatigue, but have not been used before in GIST patients.

Physicians and patients often ascribe fatigue during TKI therapy to the drug itself. Remarkably, a randomised clinical trial comparing imatinib with placebo as adjuvant treatment of GIST found comparable percentages of fatigue in both groups [5]. This indicates that factors other than imatinib use may contribute to fatigue. There is evidence for the contribution of psychosocial factors to fatigue in patients with other malignancies, both after adjuvant treatment and during palliative treatment. For example, more negative social interactions and fatigue catastrophizing thoughts predicted higher levels of fatigue after completion of adjuvant treatment [9]. Additionally, a lowered level of physical activity contributed to fatigue in patients with advanced cancer [10]. Studies in patients receiving chemotherapy have documented negative effects of psychological distress on fatigue [11]. To our knowledge, no study has investigated the contribution of these aforementioned factors to the fatigue experienced by GIST patients.
This observational study had three aims. First, the prevalence of severe fatigue in GIST patients was determined using a self-report questionnaire with a validated cut-off for severe fatigue and compared to matched healthy controls (MHCs). Most studies on cancer-related fatigue (CRF) have been limited in including GIST patients and studies focusing on GIST patients have not had fatigue as the focus of examination. Second, the impact of severe fatigue on quality of life (QoL), psychosocial variables, and physical functioning was examined. Finally, more knowledge about the correlates of fatigue can contribute to its management. Which may, in turn, also help patients to adhere to the chronic use of TKIs. Therefore, the third study aim was to explore associations between fatigue and use of TKIs, psychosocial variables, and physical functioning.

METHODS

Study population

This observational, cross-sectional study was conducted in outpatient clinics of the Radboud university medical center in The Netherlands. To equal the real-life general GIST population, 119 adult outpatients with localized or metastatic GIST who had been or were currently being treated for GIST were invited to participate in the study. Patients were categorized into three groups based on their current treatment status: (1) treatment completed (i.e. status after radical surgical resection +/- (neo)adjuvant imatinib), (2) treatment with curative intent (i.e. on active (neo)adjuvant TKI), or (3) palliative treatment and best supportive care (i.e. TKI for unresectable primary or metastatic GIST or BSC).

Data were collected in two periods. The first period ran from June-October 2012, collecting data from 55 out of 83 patients. The second period ran from January-March 2015, collecting data from 35 out of 36 patients. If patients were willing to participate, they filled in questionnaires once after they had given written informed consent. Patients who did not participate either indicated that they did not want to participate or did not respond to the request to participate in the study. The medical ethical committee of the hospital approved the study.

Matched healthy controls (MHCs, n=234) were derived from a cohort of panel members of CentERdata. CentERdata is a Dutch research institute at Tilburg University [12]. The CentERpanel is composed of more than 2000 Dutch households, representing the adult Dutch-speaking population with respect to demographic characteristics. MHCs had no sickness absence in the workplace (0 days) in the month prior to filling in the fatigue questionnaire, and were matched on age, gender, and educational level.
Measurement
MHCs completed the fatigue questionnaire and a questionnaire for demographic information. Demographic variables of patients were collected via a self-report questionnaire. Medical information of patients was retrieved from medical records. Patients completed the following questionnaires:

*Checklist Individual Strength, subscale fatigue severity (CIS-fatigue).* A large number of instruments have been developed to measure fatigue. We assessed fatigue with 8 items of the subscale fatigue severity (7-point Likert scale) of the CIS [13]. Scores range from 8 to 56. A score of 35 points or higher indicates severe fatigue, i.e. two standard deviations (SDs) above the mean of a healthy control group [13]. The CIS-fatigue has been used previously for assessing CRF [14, 15].

*EORTC Quality of Life Questionnaire (EORTC QLQ-C30, version 3.0).* QoL was assessed with five functional scales and a scale on global health-related QoL of the EORTC QLQ-C30 [16]. Total scores on each subscale are converted to a 0-100 scale. A high scale score represents a high level of functioning or a high QoL, respectively.

*Self-Efficacy Scale (SES).* Sense of control regarding fatigue was measured with the SES [17]. The SES consists of 7 items scored on a 4-point Likert scale. Higher total scores are indicative for more self-efficacy.

*Fatigue Catastrophizing Scale (FCS).* Catastrophizing in response to fatigue was measured with the FCS [18]. The FCS consists of 10 items scored on a 5-point Likert scale. Computing the mean of 10 items derives a total score. A higher total score indicates more catastrophizing.

*Hospital Anxiety and Depression Scale (HADS).* The summed total score of the HADS was used to reflect psychological distress [19]. The HADS includes 14 items scored on a 4-point Likert scale. Higher total scores are indicative for more psychological distress.

*Short-Form 36-item Health Survey (SF-36).* Physical functioning was measured with the 10-item subscale physical functioning of the SF-36 [20]. A total score is calculated ranging from 0 to 100. A high score defines more favourable physical functioning.
Statistical Analysis
Patients were matched with 234 MHCs (ratio 1:3) by precision matching with STATA/SE 12.1. Median and interquartile range (IQR) and mean and SD were used to describe variables. Independent samples t-tests and analyses of variance were used to test differences between groups on demographic variables, medical variables, and the presence of severe fatigue according to the CIS-fatigue. The impact of fatigue on QoL, psychosocial variables, and physical functioning was determined by independent samples t-tests. An exploratory multivariate regression analysis (method: enter) was conducted to determine whether receiving TKIs and/or psychosocial variables and/or physical functioning were associated with fatigue severity. All tests were two-sided with a significance level of 0.05. Data were analysed using SPSS 20.

RESULTS

Ninety patients (76% response rate) filled in the questionnaires. The final sample comprised 89 patients, as one patient was excluded since the CIS-fatigue was not completed. Data on demographic and medical characteristics of all participating patients are shown in Table 1. Participants did not differ significantly on demographic variables from non-participants (age t(116) = -.354, p = .724, gender X²(1,118) = .400, p = .527). Median age of patients was 64 years (IQR 15), 52 of them were male (58%). Median time since GIST diagnosis was 32 months (IQR 55). Surgical resection had been the primary treatment option in 62 patients (70%). At the time of participation, 61 patients (69%) received a TKI (imatinib (n=52), sunitinib (n=7), nilotinib (n=2)). Furthermore, 23 patients had completed treatment, 24 were receiving treatment with curative intent, and 42 were receiving palliative treatment (n=39) or BSC (n=3).

Prevalence and impact of severe fatigue and its correlates
Significantly more patients were severely fatigued according to the CIS-fatigue compared to MHCs, 30% versus 15% (p = .002), respectively. Mean fatigue severity was also significantly higher in patients (26.3, SD 10.8) than in MHCs (21.6, SD 13.7) (p = .004). Mean fatigue severity and the prevalence of severely fatigue did not differ significantly between the three groups, neither between patients receiving current TKIs or no TKIs (see Table 2A and 2B).

Severely fatigued patients reported significantly lower global QoL than non-fatigued patients and were more impaired on all EORTC-QLQ functional scales (see Table 3). In addition, severely fatigued patients had less favourable physical functioning, lower self-efficacy, and reported more fatigue catastrophizing and psychological distress. The correlates of fatigue are shown in Table 4. More psychological distress,
lower level of physical functioning and currently receiving TKIs were significantly associated with fatigue severity (Adjusted $R^2$ 0.58).

Table 1. Demographic and medical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients ($n=89$)</th>
<th>MHCs ($n=234$)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64 (IQR 15)</td>
<td>64 (IQR 14)</td>
</tr>
<tr>
<td></td>
<td>range = 21-86</td>
<td>range = 18-90*</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>52 (58.4%)</td>
<td>149 (63.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>37 (41.6%)</td>
<td>85 (36.3%)</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>4 (4.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Secondary</td>
<td>48 (53.9%)</td>
<td>124 (53.0%)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>37 (41.6%)</td>
<td>110 (47.1%)</td>
</tr>
<tr>
<td>Time since initial diagnosis (months)</td>
<td>32 (IQR 55)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>range = 2-204</td>
<td></td>
</tr>
<tr>
<td>Location of primary tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>43 (48.3%)</td>
<td></td>
</tr>
<tr>
<td>Small intestine</td>
<td>20 (22.5%)</td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>7 (7.9%)</td>
<td></td>
</tr>
<tr>
<td>Intra abdominal</td>
<td>3 (3.4%)</td>
<td></td>
</tr>
<tr>
<td>Duodenum</td>
<td>5 (5.6%)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>11 (12.3%)</td>
<td></td>
</tr>
<tr>
<td>Primary treatment option</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical resection</td>
<td>62 (69.7%)</td>
<td></td>
</tr>
<tr>
<td>TKI therapy</td>
<td>27 (30.3%)</td>
<td></td>
</tr>
<tr>
<td>TKI therapy at the time of participation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>61 (68.5%)</td>
<td></td>
</tr>
<tr>
<td>with curative intent ($n=22$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with palliative intent ($n=39$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>28 (31.5%)</td>
<td></td>
</tr>
<tr>
<td>Treatment status at the time of participation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment completed*</td>
<td>23 (25.8%)</td>
<td></td>
</tr>
<tr>
<td>Treatment with curative intent*</td>
<td>24 (26.9%)</td>
<td></td>
</tr>
<tr>
<td>Palliative treatment ($n=39$) or BSC ($n=3$)*</td>
<td>42 (47.2%)</td>
<td></td>
</tr>
</tbody>
</table>

MHCs = Matched Healthy Controls; IQR = Interquartile Range; TKI = Tyrosine Kinase Inhibitor; BSC = Best Supportive Care. * 84 patients could be matched with MHCs, not all patients could be matched to 3 controls; b Patients were matched with MHCs within an age range of 0-5 years; c Status after radical surgical resection +/- (neo)adjuvant imatinib; d On active (neo)adjuvant TKI; e TKI for unresectable primary or metastatic GIST or BSC.
Table 2A. Mean fatigue severity and prevalence of severe fatigue based on treatment status at time of participation

<table>
<thead>
<tr>
<th></th>
<th>Treatment completed (n=23)</th>
<th>Curative intent (n=24)</th>
<th>Palliative intent (n=42)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean fatigue severity (SD)</td>
<td>23.43 (14.73)</td>
<td>26.25 (13.70)</td>
<td>27.88 (13.10)</td>
<td>.460*</td>
</tr>
<tr>
<td>No. of severely fatigued patients (%)</td>
<td>5 (21.7%)</td>
<td>7 (29.2%)</td>
<td>15 (35.7%)</td>
<td>.498b</td>
</tr>
</tbody>
</table>

* Independent samples t-test; b Pearson’s chi-squared test. * Also including Best Supportive Care.

Table 2B. Mean fatigue severity and prevalence of severe fatigue based on receiving TKI therapy at time of participation

<table>
<thead>
<tr>
<th></th>
<th>TKI (n=61)</th>
<th>No TKI (n=28)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean fatigue severity (SD)</td>
<td>27.08 (13.10)</td>
<td>24.57 (14.91)</td>
<td>.424a</td>
</tr>
<tr>
<td>No. of severely fatigued patients (%)</td>
<td>20 (32.8%)</td>
<td>7 (25.0%)</td>
<td>.458b</td>
</tr>
</tbody>
</table>

* Independent samples t-test; b Pearson’s chi-squared test. TKI = Tyrosine Kinase Inhibitor.

Table 3. Impact of severe fatigue on psychological factors and physical functioning

<table>
<thead>
<tr>
<th></th>
<th>Non-severely fatigued patients (n=62)</th>
<th>Severely fatigued patients (n=27)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EORTC-QLQ-C30 (mean, SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global health status/QoL</td>
<td>82.0 (15.8)</td>
<td>58.3 (15.7)</td>
<td>.000*</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>89.7 (12.0)</td>
<td>68.1 (20.6)</td>
<td>.000*</td>
</tr>
<tr>
<td>Role functioning</td>
<td>82.0 (23.6)</td>
<td>61.7 (29.1)</td>
<td>.001*</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>84.0 (19.3)</td>
<td>68.2 (24.8)</td>
<td>.002*</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>89.2 (17.1)</td>
<td>66.7 (25.3)</td>
<td>.000*</td>
</tr>
<tr>
<td>Social functioning</td>
<td>89.0 (18.1)</td>
<td>63.0 (28.6)</td>
<td>.000*</td>
</tr>
<tr>
<td><strong>SES (mean, SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-efficacy</td>
<td>20.2 (3.1)</td>
<td>18.4 (3.8)</td>
<td>.017*</td>
</tr>
<tr>
<td><strong>FCS (mean, SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue catastrophizing</td>
<td>13.7 (4.4)</td>
<td>23.2 (8.3)</td>
<td>.000*</td>
</tr>
<tr>
<td><strong>HADS (mean, SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological distress</td>
<td>6.4 (4.4)</td>
<td>15.2 (7.6)</td>
<td>.000*</td>
</tr>
<tr>
<td><strong>SF-36 (mean, SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>82.3 (18.4)</td>
<td>58.0 (23.3)</td>
<td>.000*</td>
</tr>
</tbody>
</table>

* Statistically significant values (p < 0.05)

EORTC-QLQ-C30 = EORTC Quality of Life Questionnaire; SES = Self-Efficacy Scale; FCS = Fatigue Catastrophizing Scale; HADS = Hospital Anxiety and Depression Scale; SF-36 = Short-Form 36-item Health Survey.
Fatigue in patients with GIST

Table 4. Multivariate regression analysis (method: enter) to explore associations with fatigue severity

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Dependent variable: CIS-fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standardized Beta</td>
</tr>
<tr>
<td>Current TKI therapy: no vs. yes</td>
<td>.168</td>
</tr>
<tr>
<td>Self-efficacy (SES)</td>
<td>-.065</td>
</tr>
<tr>
<td>Fatigue catastrophizing (FCS)</td>
<td>.176</td>
</tr>
<tr>
<td>Psychological distress (HADS)</td>
<td>.376</td>
</tr>
<tr>
<td>Physical functioning (SF-36)</td>
<td>-.332</td>
</tr>
</tbody>
</table>

* Statistically significant values (p < 0.05)

CIS-fatigue = subscale Fatigue Severity, Checklist Individual Strength; TKI = Tyrosine Kinase Inhibitor; SES = Self-Efficacy Scale; FCS = Fatigue Catastrophizing Scale; HADS = Hospital Anxiety and Depression Scale; SF-36 = Short-Form 36-item Health Survey.

**DISCUSSION**

This study investigated the prevalence and severity of fatigue by patient-reported outcomes (PRO’s) in GIST patients. Compared to matched healthy controls, the prevalence of severe fatigue is 50% higher among GIST patients, with about one-third exceeding the cut-off for severe fatigue. Overall, mean fatigue severity and the proportion of severely fatigued patients did not significantly differ between the patients who finished treatment, patients on treatment with curative intent, and patients receiving palliative treatment or BSC, nor between patients with and without current TKIs. QoL is negatively affected by fatigue and severely fatigued patients reported worse functional, psychological, and physical well being compared to non-severely fatigued patients.

The National Comprehensive Cancer Network Guidelines on cancer-related fatigue (CRF) recommend assessment of fatigue by PRO’s and not by physicians’ ratings [21]. Previous studies in GIST patients did not assess fatigue with PRO’s. Instead, physicians rated fatigue on a numerical rating scale. In these studies, severe fatigue was seldom reported. However, physicians tend to underestimate patients' symptoms [8]. This accords with the higher prevalence of fatigue in our study. The detrimental effect of fatigue on QoL and functional, psychological, and physical well-being echoes with findings of other studies reporting on fatigue in patients with more common cancer types [22-25].
We found that receiving TKIs was significantly associated with fatigue severity. However, 26% of severely fatigued patients did not receive TKIs and 67% of patients who currently received TKIs were not severely fatigued. This supports our expectation that factors other than TKI use may contribute to fatigue. We found that more psychological distress and lower physical functioning were also related to fatigue severity. The role of physical activity in CRF is well documented. More active, physically fit patients experience less fatigue during cancer treatment than patients with a lower level of physical activity [26]. In the current study, reduced physical functioning was indeed observed in severely fatigued patients. A Cochrane review concluded that interventions focusing on exercise could be beneficial for individuals with fatigue both during and after cancer treatment [27]. GIST patients may also benefit from physical activity programs. The level of psychological distress was also related to fatigue severity. One-third of all GIST patients (34%) had a score above the recommended threshold for identifying the presence of significant depressive symptoms [19]. This psychological distress might be attributable to the recurrent nature of GIST, which may lead to high levels of fear of disease progression, as found by Custers et al. (2015) [28]. Influencing psychological distress by psychosocial interventions may also reduce fatigue in GIST patients. An example of such a psychosocial intervention is cognitive behaviour therapy focused on (fatigue-related) behaviour and beliefs which was found to be effective in reducing fatigue in patients during and after cancer treatment [14, 15].

Contrary to our expectation, we did not find an association between fatigue-related beliefs and fatigue. However, previous research has shown that these beliefs are only present in severely fatigued patients and taking into account that in absolute numbers only 27 patients in our sample were severely fatigued. Moreover, though mean fatigue severity and prevalence of severe fatigue was higher in patients receiving palliative treatment compared to patients receiving treatment with curative intent, this difference was not statistically significant. However, we had a relatively small sample, which might have increased our chance of type II error. Therefore, replication in a larger sample of GIST patients is recommended since it is not unlikely that fatigue is more severe in patients receiving treatment with palliative intent.

Further limitations should be considered. First, the cross-sectional nature of our study does not allow us to draw conclusions about causality. Second, the extent to which the findings of this study can be generalized to all patients with GIST is limited by the relatively small sample size. The small sample size also limited our ability to study other potential correlates of fatigue in our exploratory regression analysis, such as pain or sleep dysfunction. Studies on fatigue in GIST patients would be strengthened if future investigators unite their efforts and collect larger samples of PRO’s. As a result of change in study personnel, data were collected in two distinct time periods.
Nevertheless, no relevant differences in treatment or other aspects during this interval existed that could have affected the combined study sample. Although we collected data from a heterogeneous sample for this exploratory study, a more homogenous sample could be a useful augment to future studies investigating fatigue within each GIST patient category. For example, heterogeneity in treatment modalities, length of treatment, dosage level, and extent of disease may also affect the presence and severity of fatigue within each patient group. While there was diversity in current treatment status, the majority of participants were on TKIs. Finally, information on comorbidity was not available for both GIST patients and MHCs. In MHCs, we used the criterion of no sickness absence in the workplace as a proxy for being healthy. However, this does not rule out the possibility of having symptoms or comorbidities with which they would still attend work.

Bearing in mind that GISTs are rare tumors and research focusing on the experience of severe fatigue is lacking, the present research is an important first exploratory study. This research showed that severe fatigue is a relevant and disabling symptom for almost one-third of GIST patients. Patient-reported fatigue severity is associated with TKI use. Yet, if physicians keep interpreting the presence of fatigue as solely TKI-related, as a result, both physician and patient may feel they cannot influence the fatigue. The present study adds valuable knowledge by showing that next to TKI use, lower physical functioning and more psychological distress are also associated with fatigue. Physicians could play a crucial role in informing patients about these associated factors of fatigue that deserve appropriate management.
REFERENCES


CHAPTER 4

ADAPTING AN EVIDENCE-BASED INTERVENTION TO ADDRESS TARGETED THERAPY-RELATED FATIGUE IN CHRONIC MYELOID LEUKEMIA PATIENTS

Hanneke Poort, Cathy Meade, Hans Knoop, Marieke Gielissen, Javier Pinilla-Ibarz, Paul Jacobsen

Cancer Nursing, 2016; Epub ahead of print

1 This study has been performed at H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, United States.
ABSTRACT

Background
Fatigue is one of the most important quality of life issues experienced by patients being treated with oral targeted therapy for chronic myeloid leukemia (CML). Yet, no intervention exists that specifically addresses strategies to reduce targeted therapy-related fatigue. This study adapted an evidence-based clinic-delivered intervention (EBI) ‘cognitive behavior therapy for post-cancer fatigue’ for use in CML patients. The existing EBI was based on six established perpetuating factors of fatigue (i.e., Sleep, Activity, Helpful Thinking, Coping with Cancer, Social Support, Fear of Disease Recurrence). Study aims were to gauge reactions to (1) existing content and (2) a new Internet-assisted intervention delivery format.

Methods
Guided by the ADAPT-ITT framework, we used a series of systematic steps and adaptation methodologies, including semi-structured interviews with CML patients and providers, and feedback from topical experts.

Results
Patients were receptive to existing content topics and an Internet-assisted delivery format was acceptable. A key theme reflected the need for a new customized psycho educational module about CML as a disease and its treatment. Both providers and patients held positive views about the potential of the adapted EBI to improve fatigue.

Conclusion
Findings offered essential guidance for the adaptation and reinforced the utility of the adapted intervention. Adapting existing EBI’s for new audiences contributes to advancing findings of evidence-based research, ultimately providing nurses and other health care providers with important referral options to interventions that may provide useful strategies to improve quality of life and reduce targeted therapy-related fatigue.
Adapting a fatigue intervention for patients with CML

INTRODUCTION

Survival in patients with chronic myeloid leukemia (CML) improved considerably following the introduction of the first tyrosine kinase inhibitor (TKI) imatinib [1]. Although TKIs revolutionized treatment of chronic phase CML, they may need to be taken indefinitely and on a daily basis [2]. Accordingly, with the growing use of maintenance therapy in certain forms of cancer, CML has become a chronic condition. The transition from short-term active treatment to potentially lifelong maintenance treatment brings attention to finding ways to manage common side effects such as fatigue and pain. Although evidence-based interventions for managing these side effects are available for cancer patients during or after short-term active treatment [3,4], they are not designed for and have not been tested for efficacy in the expanding number of patients who are receiving maintenance treatment with TKIs.

To address the need for an intervention that supports CML patients in managing their health during maintenance TKI treatment, we have built upon a previously empirically supported version of a therapist-delivered cognitive behavioral program for disease-free cancer patients [5] that specifically addresses one of the most common and debilitating side effects, that is fatigue. In this paper, we describe processes used to adapt an existing evidence-based intervention for application in CML patients with targeted therapy-related fatigue. Beyond this immediate goal, the current report seeks to illustrate an approach that can be applied to other existing evidence-based interventions for improving the lives of cancer patients.

As background, fatigue proves to be one of the five most severe side effects in CML patients who are prescribed TKIs, alongside drowsiness, disturbed sleep, muscle soreness and cramping, and trouble remembering things, with one-third of patients reporting persistent moderate-to-severe symptoms [6]. Additionally, compared to age-matched controls with no history of cancer, patients with CML who take a TKI report significantly worse fatigue severity and fatigue interference [7]. Moreover, fatigue is the most important factor that limits quality of life of CML patients [8]. Treatment of fatigue is particularly relevant as chronic side effects may affect adherence to TKI treatment, and adherence is a critical factor to ensure appropriate molecular responses [9].

Despite the acknowledged importance of this symptom, there are no published intervention studies addressing targeted therapy-related fatigue. However, previous research has demonstrated the efficacy of cognitive behavior therapy (CBT) designed for treating post-cancer fatigue [5,10]. The conceptual framework for the intervention developed by the Expert Center for Chronic Fatigue (Nijmegen, The Netherlands) is a model that distinguishes factors that precipitate fatigue from factors that perpetuate...
fatigue [11]. The underlying assumption is that cancer treatment and/or the disease itself may trigger fatigue (precipitating factors), but that other factors such as sleep disturbance, physical inactivity, and fear of disease recurrence are responsible for the persistence of fatigue (perpetuating factors). As such, CBT for post-cancer fatigue is a tailored, individual-based, clinic-delivered intervention that itself was adapted from the original CBT for chronic fatigue syndrome developed by the Expert Center for Chronic Fatigue [12]. CBT for post-cancer fatigue sessions cover six possible perpetuating factors (the ‘Modules’): Sleep, Activity, Helpful Thinking, Coping with Cancer, Social Support, and Fear of Disease Recurrence (see Table 1 for a description of existing intervention modules). Evidence supports the efficacy of CBT for post-cancer fatigue in decreasing severe fatigue and functional impairment [5,10]. Based on this evidence, it is now among the recommended interventions for addressing fatigue in disease-free cancer survivors in guidelines issued by the American Society of Clinical Oncology [13].

Table 1. Description of existing intervention modules of the original evidence-based intervention CBT for post-cancer fatigue

<table>
<thead>
<tr>
<th>Module</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Sleep</td>
<td>Patients are encouraged to maintain a regular sleep-wake pattern seven days a week with fixed bed and wake-up times and no daytime napping. If needed, attention is paid to additional sleep hygiene practices.</td>
</tr>
<tr>
<td>(2) Activity</td>
<td>A distinction can be made between patients with fluctuating patterns of activity (i.e. bursts of activities followed by inactivity) and patients with a pattern of persistent inactivity. First, patients with fluctuating patterns establish a base level by evenly distributing their level of activity over the day. Upon reaching this base level, a graded activity program (e.g. walking) is started. Patients with persistent inactivity will start the graded activity program immediately.</td>
</tr>
<tr>
<td>(3) Helpful Thinking</td>
<td>Dysfunctional fatigue-related cognitions [5] (e.g. catastrophizing, low self-efficacy, or unhelpful attributions) are discussed and more helpful ways of thinking are taught.</td>
</tr>
<tr>
<td>(4) Coping with Cancer</td>
<td>Insufficient coping with cancer and/or its treatment [5] is targeted by talking or writing about these experiences (exposure) in order to help patients to process the experiences and improve coping skills.</td>
</tr>
<tr>
<td>(5) Social Support</td>
<td>Some patients perceive a discrepancy between actual and desired social support, experience negative social interactions or have unrealistic expectations of others. These patients are helped to instil more realistic expectations toward their social support group and to communicate more assertively with others with respect to their current abilities.</td>
</tr>
<tr>
<td>(6) Fear of Disease Recurrence</td>
<td>Some patients experience excessive fear of disease recurrence. Their fears and thoughts are discussed with a focus on how to deal with the uncertainty about their future health. Dysfunctional beliefs are challenged and it is discussed how to reduce ruminating about the possibility of disease recurrence.</td>
</tr>
</tbody>
</table>
Table 2. Adaptation Plan for CBT for targeted therapy-related fatigue modelled after ADAPT-ITT

<table>
<thead>
<tr>
<th>Phases</th>
<th>Methodologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Assessment:</strong> What is the need?</td>
<td>Conduct needs assessment of CML patient audience. The literature reviewed clearly demonstrates the need to develop an intervention to address targeted therapy-related fatigue.</td>
</tr>
<tr>
<td>2. <strong>Decision:</strong> What evidence-based intervention is selected?</td>
<td>Decision to adapt the CBT for post-cancer fatigue. Initial English-language translation of original therapy manual created using services of a professional translator.</td>
</tr>
<tr>
<td>3. <strong>Administration:</strong> What needs to be adapted and what added?</td>
<td>Conduct in-depth interviews with CML patients reporting targeted therapy-related fatigue, including response to use of internet-assisted delivery channel. Conduct in-depth interviews with CML health care providers. Analyse results to inform next steps.</td>
</tr>
<tr>
<td>4. <strong>Production:</strong> How to produce and draft the evidence-based intervention?</td>
<td>Develop adaptation plan and table of modified text and/or new activities. Draft adapted evidence-based intervention and therapy manual to balance fidelity of core elements, underlying conceptual framework, and internal logic pathways. Document adaptations according to content, context, and concepts, language, and persons.</td>
</tr>
<tr>
<td>5. <strong>Topical experts:</strong> Who are the experts?</td>
<td>Engage topical experts who developed the original CBT for post-cancer fatigue to ensure input, feedback and review of CBT for targeted therapy-related fatigue drafts.</td>
</tr>
<tr>
<td>6. <strong>Integration:</strong> What is going to be included in the adapted evidence-based intervention?</td>
<td>Integrate feedback and data from topical experts. Draft new CBT for targeted therapy-related fatigue therapy manual and program components with attention to fidelity, fit and congruence to original evidence-based intervention. Review findings with topical experts and make final decisions and revisions. Finalize measures to be used to assess perpetuating factors.</td>
</tr>
<tr>
<td>7. <strong>Training</strong></td>
<td>Training of staff to implement CBT for targeted therapy-related fatigue involves the therapists reviewing the CBT therapy manual and rehearsing intervention elements in modelling and role-playing sessions with simulated patients. This 3-day in-person training was created and delivered by the topical experts.</td>
</tr>
<tr>
<td>8. <strong>Testing:</strong> Was the adaptation successful?</td>
<td>Test adapted CBT for targeted therapy-related fatigue and evaluate efficacy in ongoing pilot randomized controlled trial.</td>
</tr>
</tbody>
</table>

CBT = Cognitive Behavior Therapy; CML = Chronic Myeloid Leukemia.

The current report describes a series of systematic steps and processes to adapt and modify an existing evidence-based intervention in response to the needs of another patient population. The process of modifying an evidence-based intervention without changing the intervention’s core elements and internal logic is often referred to as ‘adaptation’ [14]. Instead of starting over and expending scarce resources, adapting existing evidence-based interventions has the potential to accelerate the translation of research into practice, thus providing health care professionals and patients with treatment options for new patient target groups. The adaptation process allows for changing context in terms of structure, intensity, format, metaphors, goals etc., while maintaining essential theoretical fidelity and fit. To guide the adaptation process, we developed a plan drawn from the adaptation literature [14-19], our prior experience in creating, trans creating and adapting interventions [20-24], the NCI’s Stages in Health...
Chapter 4

Communication Model [25], and the ADAPT-ITT Model [26]. Table 2 summarizes our plan modelled after the ADAPT-ITT model that includes 8 phases: (1) Assessment; (2) Decisions on evidence-based intervention selection; (3) Administration – What needs to be adapted; (4) Production; (5) Topical experts; (6) Integration; (7) Training and (8) Testing. This paper focuses primarily on the initial steps and methodologies (1-6), which provided the necessary foundation for informing the adaptation. The details on the training and specific results of the pilot study (steps 7 and 8), once complete, will be reported in the future.

As described in the upcoming sections, the adaptation process described here represents a series of sequential phases and steps that advance an idea in response to a patient need, to a final testing and evaluation phase. In our case, this adaptation was predicated on the need for an intervention that offered strategies for patients with CML to ameliorate targeted therapy-related fatigue. The adaptation described here also involves moving from a clinic-based face-to-face delivery during a 6-month period (bi-weekly sessions) to Internet-assisted delivery format using video telephony and tablet computer technology (i.e. FaceTime using iPads) during an 18-week period (weekly sessions) to reduce travel burden. Therefore, as part of our adaptation plan, we also sought to gauge CML patients’ interest in, and acceptability of, delivery channel, duration, and frequency of CBT for targeted therapy-related fatigue.

METHODS

Phase 1 and 2 - Assessment and Decision
Our approach builds upon a previously effective evidence-based intervention for post-cancer fatigue [5] and an established patient need [8]. We were not proposing to develop a de novo intervention. Rather, the program builds on an existing intervention comprised of six modules, based on the precipitating-perpetuating model for fatigued disease-free cancer patients [5,10].

Phase 3 - Administration (what needed to be adapted?)
As part of the adaptation process, we conducted in-depth interviews with CML patients and providers. Next, findings were summarized and implications for adaptation of the existing evidence-based intervention were formulated in close collaboration with topical experts (i.e. developers of the original evidence-based intervention). Then, the original therapy manual and training materials were revised through intensive iterative back/forth communications among research members to incorporate feedback from patients and providers.
Participants and Procedures
Eligible patients were ≥18 years old, able to speak and read English, diagnosed with chronic phase CML, not previously treated for other cancer (except non-melanoma skin cancer) in the past 2 years, under the care of a Moffitt Cancer Center physician, and on a TKI for ≥ 3 months. In addition, patients had to report moderate-severe fatigue in the past week as reflected by a Fatigue Symptom Inventory score of ≥ 4 [27]. Patients were excluded if they had a clinical condition or disease (e.g. anemia or multiple sclerosis) that could account for the presence of moderate-severe fatigue. Potential patient participants were identified via review of medical records and appointment schedules by study coordinators. Identified patients were telephoned 1 week before their next appointment to explain study procedures and screened for fatigue. Eligible patients that gave written informed consent were asked to stay after their appointment to be interviewed.

Eligible providers were staff members in the Department of Malignant Hematology at Moffitt Cancer Center who cared for CML patients as a Medical Doctor, Advanced Registered Nurse Practitioner, Physician Assistant, or Registered Nurse. CML patients at Moffitt Cancer Center are treated by a limited sample of providers. Provider participants were identified and then invited for participation via e-mail. Eligible providers that gave written informed consent were scheduled for an interview.

Instrumentation and Data Collection
Preceding the interview, patients provided demographic information (e.g. age, gender, race, ethnicity, marital status, and education) by completing a self-report form. Clinical information (e.g. CML diagnosis date, current TKI start date, and previous TKI [if applicable]) was collected via medical chart review.

Patient and provider semi-structured interview guides were developed by two of the study investigators (PJ and CM) based on relevant literature, their clinical experiences, and discussion with the topical experts (HK and MG). The guides consisted of questions about: (1) general thoughts about fatigue in relation to TKIs and CML; (2) general thoughts about TKIs and CML (the provider guide had some additional questions to evaluate the type of education provided to patients before the start of TKI therapy); (3) overall reaction to CBT for targeted therapy-related fatigue program; (4) usefulness and ranking of existing modules; (5) other useful topics; and (6) reaction to Internet-assisted delivery channel (i.e. FaceTime using iPads), duration, and frequency of CBT for targeted therapy-related fatigue. To help elicit feedback about the existing six modules, the interviewers had the modules listed on cards. This made it easier to respond to each module one at a time and gather feedback. It also helped to facilitate ranking of the modules in terms of relative importance. New topics were also solicited.
Two behavioral scientists (PJ and CM) with extensive interviewing experience conducted the individual interviews with patients and providers using the interview guides. Regarding the sample size for the patient interviews ($n=10$), we were guided by the concept of data saturation, which was defined in this study as the point that no new insights or themes were observed [28]. Our research team continually assessed the adequacy of this sample in terms of quality, comprehensiveness, and richness of information [29]. For example, was there sufficient depth of information to adequately inform the adaptation of the evidence-based intervention and at which point were no new insights observed. In addition to the number of interviews, the team also considered the amount of time spent with each CML patient (up to 60 minutes) when defining data saturation and stopping data collection [30]. In terms of health care providers, our sample was defined (and somewhat limited) by the existing number of providers ($n=4$) at our institution who cared primarily for patients with CML. Albeit small, it was felt that this sample well represented the required perspectives to address potential modifications for the adapted evidence-based intervention. Time spent with providers was approximately 40 minutes. All interviews were audio-recorded and transcribed by a local professional transcriptionist with experience in qualitative health research. Each patient received $50 and each provider received $35 for participating. Liberty Institutional Review Board, a central independent review board, approved the study.

**Data Analyses**

All interviews were transcribed verbatim. Data transcripts were manually coded using directed content analysis techniques to extend and refine existing theory on CBT for post-cancer fatigue to CBT for patients experiencing targeted therapy-related fatigue [31]. Codes were generated and refined before and during data analysis using a series of iterative processes by two study researchers (HP and CM). First, the researchers created an initial codebook based on a priori (deductive) codes drawn from existing theory, the interview guides and research questions. The researchers then reviewed all transcripts carefully, highlighting all passages that described relevant data. All highlighted passages were coded using the predetermined codes. Any text that could not be coded into one of these initial codes was given a new inductive code (e.g. ‘impact of fatigue’ for descriptions of how fatigue impacted areas of daily living) [31]. The same researchers independently hand-coded the transcripts, compared codes, and resolved discrepancies through consensus, to reach an optimal inter-rater agreement (95%) [32]. The data were summarized through descriptive summaries and data display matrices, in which supportive and expanded views of the existing CBT for post-cancer fatigue were identified. A summary listing of module content rankings was also included. The authors reviewed, validated, and verified interpretations, and study conclusions via weekly calls with topical experts. Representative, participant responses were selected to illustrate key findings.
RESULTS

Of the initial 12 eligible patients who were approached for participation, one was found ineligible after consent and one declined to be interviewed; consequently, 10 patient interviews were conducted in total. Four providers were approached and consented for participation. The mean age of patient participants was 53 years (range 37 to 70 years), 60% was male, and 70% Caucasian/30% African American. The majority of patients was employed, married and had some college education. The sample included patients with varying disease and treatment duration. Median time since diagnosis was 6.5 years (range 4 months to 10 years) and median time on current TKI was 11 months (range 3 months to 6 years). Ninety per cent of patients had used at least one TKI previously. The most frequently used current TKIs were nilotinib (50%) and dasatinib (40%).

Findings from patient and provider interviews

Illustrative quotations from patients and providers are incorporated in the text in italics.

Thoughts about patients’ fatigue

Patients commonly described fatigue as ‘crushing’, being ‘worn out’ or ‘whipped out’, and having ‘zero energy’ or feeling ‘dead’. Some patients related that they ‘cannot get out of bed in the morning’ others just ‘crash at the end of the day’. Fatigue impacts patients in a number of ways, most significantly seen in the change or reduction of social, family, and physical activities. In general, patients felt that their family members are supportive and understanding. Patients indicated that they do not often bring up fatigue to their providers. Most patients felt their providers think fatigue is a normal side effect of TKIs.

Providers acknowledged fatigue as a common complaint, reported by an estimated 70% or more of their CML patients. As such, most providers usually follow up on this concern by discussing sleep patterns, encouraging physical activity, or changing TKIs when more side effects are present.

Thoughts about patients’ medication and CML

A number of general thoughts about CML emerged. Considering that most patients wished they did not have a form of cancer at all; some patients described feeling very fortunate for having this type of cancer, since they felt ‘It’s the best one to have’. Alternatively, some patients felt guilty for doing well and looking so healthy compared to other patients seen at the Cancer Center. They stated that they ‘don’t look sick’. Most patients experienced a range of side effects from the TKIs (e.g. fatigue, nausea, diarrhea, joint pain, and muscle cramp), but related no intentional dose skipping as
they felt the TKI is ‘keeping me alive’ and is their ‘life preserver’. Unintentional dose skipping was reported by patients, mostly forgetting the second evening dose of nilotinib due to falling asleep. An overwhelming majority of patients clearly attributed their fatigue to the use of TKIs. In fact, only one patient did not specifically attribute fatigue to TKI use per se but rationalized the presence of fatigue with other factors (i.e., unhealthy diet, low level of physical activity, being overweight, and under stress). In addition, this patient explained that it was difficult to indicate whether the fatigue was related to TKI use since ‘I have been on a TKI for so many years and then I am ten years older’.

Providers thought intentional dose skipping due to side effects does occur in a few patients. All providers had the impression that patients attribute their fatigue to TKI use, and they inform patients about fatigue as a known side effect of all TKIs when initiating treatment.

**Overall reaction to CBT for targeted therapy-related fatigue**

Patients and providers had a positive attitude toward the intervention; thinking it is ‘worthwhile’, ‘great’, ‘a very novel approach’, and would be ‘helpful’ for fatigued patients. Several patients stated that ‘It is a good idea’ and one patient further elucidated ‘If we can help people out that would be very good, fatigue affects everything’. Overall, patients were highly positive and expressed being interested in and open to actually using the intervention. One patient preferred simply an email with information, not an intensive interaction with a therapist using video-telephony.

**Usefulness and ranking of the existing modules**

The majority of patients considered all six modules highly useful. The module **Sleep** currently applied to almost all patients, with waking up too early, falling asleep during the day, or not being able to sleep at bedtime being commonly reported. The module **Activity** applied to all but one patient. Patients experienced reduced or fluctuating activity patterns and considered this module highly pertinent. Most patients reported that the module **Helpful Thinking** about fatigue was not as applicable to them. Some patients did have hopeless thoughts such as ‘There is nothing I can do’ and ‘I just need to accept it’, but these thoughts did not seem to impact their everyday functioning. There were a variety of reactions when patients were asked about the module **Coping with Cancer**. More than half of the patients had no major concerns, accepting their situation and saying ‘It is what it is’. Yet, many identified that some thoughts and emotions were triggered before 3-monthly monitoring visits or in case of bad lab results. Reactions from patients who did report concerns ranged from ‘Why do I have this disease?’ and ‘How would I cope with it if I ever get to the point where it gets really bad’, to struggling with knowing that not taking the TKI would make them feel better but worsen their disease status. A few struggled with integrating the strict medication
Adapting a fatigue intervention for patients with CML

regimen into daily life. Although the majority of patients indicated already receiving good support, they did consider the module Social Support a useful topic to discuss. A few patients reported changes in social support (e.g. people distancing from them) or unpleasant social interactions (e.g. being called ‘lazy’ when they were just too tired to do things). The majority of patients did not experience current issues that would be addressed in the module Fear of Disease Recurrence, but felt the module could be useful for others. In fact, patients found the term ‘disease recurrence’ confusing and instead referred to ‘increased disease activity’. An explanation for this is that a response evaluation in CML is determined by the value of a molecular marker (i.e. BCR-ABL transcript), instead of determining ‘recurrence’ of a solid tumor in patients of the original evidence-based intervention’s population. CML is often considered a slowly progressing disease with long periods of stability. Hence, the terms and language used needed to be edited to better reflect the experience of patients with CML. Even though most patients felt their disease was well controlled and felt that they did not currently need this module, thoughts about increasing disease activity did occur once in a while, mostly triggered by medical appointments or upcoming blood tests. However, some patients worried more about their future health. One patient stated ‘Ever since I was diagnosed, I’m waiting for the other shoe to drop’ and later on ‘For the first couple years I really did feel that, I had maybe a short period of time, I didn’t think that I would live that long and so that was a concern and it certainly impacted the way I was living my life’. Another patient expressed having thoughts about increase in disease activity all the time, especially after the last switch of TKIs, and expressed ‘I still have people who depend on me’. One patient mentioned the scary aspect of ‘dying at a young age’. In summary, the majority of patients felt all the topics were important for inclusion in the intervention, but the highest priority ones were identified as: Activity, Sleep, and Coping with Cancer. If any module did not apply to them now, all were open to future discussions.

In all, providers considered the content of the six modules useful. One provider did not recognize disrupted sleep/wake patterns as a problematic issue within this patient group. Reactions to the usefulness of the module on fear of disease recurrence (or ‘increased disease activity’) varied among the providers. Some providers thought the content of this module would be more helpful for patients that needed to switch TKIs as a result of increased disease activity compared to patients with stable disease. In addition, one provider wondered about patients’ understanding of treatment response and stated: ‘The tests that we use to measure whether they are having a good response are very confusing to patients. It’s a lot of technical lingo’. According to providers, the most relevant topics were Activity, Helpful Thinking, and Sleep/ Coping with Cancer, with the latter two topics being ranked equally.
Other useful topics

Patients mentioned several suggestions for additional topics, including more information on CML and TKIs, nutrition, and impact of CML and fatigue on personal relationships. Providers considered general information about CML and TKIs potentially useful, suggested support groups for fatigued CML patients, and raised fertility issues in younger patients. Some of these topics may be useful in other patient education venues outside of the current intervention.

Reactions to internet-assisted delivery, duration, and frequency of CBT for targeted therapy-related fatigue

Overall, patients were very receptive to intervention delivery via video-telephony (i.e. FaceTime using iPads). Duration and frequency of CBT for targeted therapy-related fatigue (i.e. 18 weeks, weekly sessions) was acceptable to patients. All patients were familiar with the Internet; most were daily users. One patient expressed a preference to meet the therapist in-person prior to starting the Internet-assisted intervention. Providers had some mixed feelings from a technology perspective; it was thought that older patients might be less receptive to the Internet-assisted delivery channel. However, we found no differences in the views of younger and older patients regarding their acceptability and interest in the Internet-assisted delivery channel.

Phases 4, 5 and 6 – Production, Topical Experts and Integration

Data and information obtained from the interviews were used to draft a creative brief. A creative brief is a well-identified summary/blueprint of findings that helps to inform the adaptation of the intervention. Table 3 displays the summary of interview findings with adaptation implications and was used to guide the modifications. The goal was to create a therapy manual for therapists that described the process of CBT as applied to patients with targeted therapy-related fatigue and CML and to provide a description of what should be covered in each module. The research team and topical experts (i.e. study consultants who had developed the original evidence-based intervention) then began integrating findings into the therapy manual. The original therapy manual consists of several components: the first section gives an introduction to CRF, followed by an explanation of the model of perpetuating factors, a section on diagnostic measures for each perpetuating factor, and separate sections describing the content of each module. The research team and topical experts had weekly conference calls over a 16-week period to examine each component of the original manual to identify areas to modify, delete, or adapt content based on feedback from the patients and providers. For example, replacing ‘fear of disease recurrence’ with ‘fear of increased disease activity’. In addition, not all existing case vignettes and quotes in the therapy manual (original vignettes were geared toward disease-free cancer patients) were pertinent for CML patients. Therefore, these were replaced with vignettes and quotations derived from the interviews that better
Adapting a fatigue intervention for patients with CML

reflected everyday experiences of CML patients. Feedback about the proposed Internet-assisted delivery channel (i.e. FaceTime using iPads) from patients and providers was generally positive. Some providers felt that elderly patients might be less receptive to Internet-assisted delivery, but previous studies indicated that elderly (cancer) patients appear to participate readily in Internet-assisted self-management programs [33,34]. Furthermore, no differences were found between younger and older patients in our sample with regard to openness to Internet-assisted intervention delivery, if they were given instructions. Based on discussion with the topical experts and due to a comment by one of the patients, the first intervention session would be delivered in-person to facilitate therapeutic alliance.

Phases 7 and 8 - Training and Testing
Once the therapy manual was finalized, the topical experts created and delivered a 3-day in-person training to prepare two therapists for delivering the intervention (HK and HP). This training included both theoretical background and rationale for each of the intervention modules, familiarizing therapists with intervention delivery, role playing with simulated patients, and discussing video recordings of provider-simulated patients’ interactions with feedback from a topical expert. The testing of the Internet-delivered CBT for targeted therapy-related fatigue is currently being evaluated in a pilot RCT conducted to determine if the intervention can effectively reduce fatigue in patients receiving maintenance treatment for CML.

DISCUSSION

The success of targeted therapy in cancer has improved the overall survival of CML significantly and transformed CML to a chronic disease. Yet many patients suffer from targeted therapy-related fatigue. Thus, an Internet-assisted intervention titled ‘Cognitive Behavior Therapy for Targeted Therapy-Related Fatigue’ was developed through an adaptation process to address this need. In general, patients and health care providers felt that all existing modules were relevant (to varying degrees), and had the potential to improve patients’ fatigue while on maintenance TKI treatment.

Our results underscore the importance of a patient-tailored approach of selecting intervention modules. In CBT for targeted therapy-related fatigue, therefore, diagnostic assessment instruments will be used to determine which modules should be included and enhanced in the CBT for a particular patient. The CBT will vary only in which modules will be addressed, but within each module the therapy is standardized. For example, the module on fear of increased disease activity only pertained to a minority subset of patients; as such not all patients will receive that module as part of the
Table 3. Summary of findings and adaptation implications for CBT for targeted therapy-related fatigue

<table>
<thead>
<tr>
<th>Interview Findings</th>
<th>Implication(s) for Adaptation</th>
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</thead>
<tbody>
<tr>
<td>Thoughts about patients' fatigue</td>
<td></td>
</tr>
<tr>
<td>· Fatigue is described as 'crushing', being 'worn out', feeling 'dead' or having 'zero energy'. The most significant impact of fatigue is seen in the change or reduction of physical, mental, and/or social activities.</td>
<td>· Descriptions are highly congruent with fatigue experienced by cancer survivors. Integrate specific quotations in the CBT for targeted therapy-related fatigue therapy manual to illustrate specific impact of fatigue for the patient with CML.</td>
</tr>
<tr>
<td>Thoughts about patients' medication and CML</td>
<td></td>
</tr>
<tr>
<td>· Patients experience a range of side effects; some of these interfere directly with sleep quality (e.g. PM dose side effects, very early AM dose) or social activities (e.g. fasting requirements before/after intake of TKIs interfering with having dinner with friends).</td>
<td>· Discuss individual side effects and patients' perspectives towards TKI during the first intervention sessions.</td>
</tr>
<tr>
<td>· Intentional dose skipping as a result of side effects was not reported by patients. Providers felt that this does occur in some patients.</td>
<td>· Emphasize to patients that adherence to TKIs is needed during CBT to conclude if CBT for targeted therapy-related fatigue is effective, but increasing adherence itself is not a goal of the current intervention.</td>
</tr>
<tr>
<td>· Patients clearly attributed fatigue to TKI use, but are willing to discuss potential perpetuating factors of fatigue ('modules').</td>
<td>· Retain model of precipitating and perpetuating factors of fatigue as rationale for the intervention.</td>
</tr>
<tr>
<td>· Patients reported both positive (i.e. grateful; 'best kind of cancer to have') and negative (i.e. guilt; 'I look so healthy comparably') feelings about having CML.</td>
<td>· Incorporate and address both ways of looking at CML in the Helpful Thinking module.</td>
</tr>
<tr>
<td>Overall reaction to CBT for targeted therapy-related fatigue program</td>
<td></td>
</tr>
<tr>
<td>· Patients and providers had a positive attitude toward the intervention.</td>
<td>· Retain the envisioned program with adaptations for targeted therapy-related fatigue in CML patients.</td>
</tr>
<tr>
<td>Usefulness and ranking of the existing intervention modules</td>
<td></td>
</tr>
<tr>
<td>· Activity, Sleep, and Coping with Cancer Treatment were considered most relevant to patients. Providers considered Sleep, Activity, Helpful Thinking and Coping with Cancer Treatment most relevant.</td>
<td>· Emphasize the existence of a module for Activity, Sleep, and Coping with Cancer treatment in the first intervention session in order to increase patient motivation.</td>
</tr>
<tr>
<td>· The term 'Fear of Disease Recurrence' does not apply to a high degree due to the chronicity of CML.</td>
<td>· Replace 'Fear of Disease Recurrence' with 'Fear of Increased Disease Activity'.</td>
</tr>
<tr>
<td>· Thoughts of disease progression occur mostly before 3-monthly monitoring visits or in case of inconsistent lab results. Providers feel that patients who need to switch TKIs due to progression or intolerance experience more anxious feelings.</td>
<td>· Address coping strategies within Fear of Disease Recurrence module. Careful attention for this topic in patients who have switched TKIs multiple times.</td>
</tr>
<tr>
<td>· All 6 intervention modules were considered useful by patients and providers, but variation in personal applicability and relevance exists, reinforcing the value of a 'tailored' intervention approach.</td>
<td>· Retain all 6 intervention modules and continue tailoring of indicated modules to each participant. Incorporate specific quotations in the CBT for targeted therapy-related fatigue therapy manual to illustrate specific impact on CML patients and draw examples for the proposed case vignettes.</td>
</tr>
</tbody>
</table>
### Other useful topics

- Patients wanted to receive more information about CML and TKIs. Providers indicated that the tests they use to measure treatment response are quite difficult to understand for patients.
- Some patients had difficulties with distinguishing normal fatigue from targeted therapy-related fatigue.
- Some patients experienced intimacy issues and/or mood swings and irritability due to fatigue.
- Impact of patients’ fatigue and impairments on significant others.
- Balancing several life domains with a limited energy level.
- Nutritional concerns (e.g. lack of appetite, fasting requirements).

- Add new psycho education module ‘understanding CML and TKI treatment’ focusing on understanding of their disease, medication, and monitoring of disease and treatment response.
- Retain as one of the interventional aims; normalize the experience of ‘healthy’ fatigue.
- Both topics are known secondary symptoms of fatigue and will be discussed during the first or second intervention session, if applicable.
- Retain the element of having significant other attend at least one session to explain aim and rationale of intervention.
- Retain the variation in activities in several domains addressed in the Activity module.
- No implications for adaptation, this is not a part of the current intervention, but may be useful in other patient education venues.

### Reaction to Internet-assisted delivery, duration, and frequency of CBT for targeted therapy-related fatigue

- All participants were familiar with using the Internet and receptive to CBT for targeted therapy-related fatigue delivery via video telephony.
- Frequency and duration of CBT for targeted therapy-related fatigue were acceptable to participants.
- Patients expressed different preferences with respect to timing of the weekly sessions.
- One participant preferred meeting the therapists in person first, before start of video telephony delivery of CBT for targeted therapy-related fatigue.
- Providers had some reservations with respect to delivery channel in the elderly patients, due to technology aspects.

- Maintain intended use of video telephony (i.e. FaceTime) for intervention delivery.
- Retain frequency and duration of CBT for targeted therapy-related fatigue.
- Incorporate flexibility in scheduling of weekly sessions (morning, afternoon, evening, weekends).
- First intervention session with the therapists will be done in person at the treatment facility, contrary to our plans to shift completely to an Internet-assisted delivery.
- Incorporate on-site instructions and testing of FaceTime following the first intervention session for all patients. Have a contact person available for patients during the intervention period.

CBT = Cognitive Behavior Therapy; CML = Chronic Myeloid Leukemia; TKI = Tyrosine Kinase Inhibitor.
intervention. Further, although the standard term in the literature ‘fear of disease recurrence’ typically applies to patients who have completed treatment for early-stage solid malignancies, patients suggested changing this term to ‘fear of increased disease activity’, an issue more relevant to patients who are on maintenance treatment to control their disease.

Our study suggested that patients had a need for more information about their disease and treatment. Therefore, the most significant change to the existing therapy manual was the development of a new psycho-education module ‘understanding CML and TKI treatment’ to address this need. This module gauges patients’ overall understanding of their disease and treatment, together with a better acceptance of the long-term nature of the treatment needed. An interactive approach was determined to be most suitable for this module. Patients are asked questions about their understanding of CML and its treatment, and the therapist checks or verifies whether this accords with general factual knowledge. Content accuracy was guided by Guidelines Insights for CML from the National Comprehensive Cancer Network [2], patient information material about CML from the American Cancer Society [35], and peer-reviewed literature [36]. If patients have further questions, they would be referred to their health care provider.

The current study confirmed the utility of using a systematic process for adapting an evidence-based intervention. In particular, the use of the ADAPT-ITT model provided a number of features that allowed for ongoing input from multiple key stakeholders (i.e. patients, providers, topical experts, and research team members). However, we note that due to the nature of the formative research among patients with CML, we only interviewed a relatively small sample of participants from a single comprehensive cancer center. The sample of 4 health care providers at one institution, albeit limited perspectives, offers an exceedingly important snapshot of the views of nurses and other health care providers who primarily care for and are highly familiar with the needs and concerns of patients with CML. In this study, the adaptation process was greatly enriched by the topical experts who had developed the ‘original’ evidence-based intervention, and their involvement was a significant strength to the process. Not only was their input essential in the development of the adapted therapy modules and manual, but their engagement also enabled us to train therapists in-person on how to deliver the core elements of the adapted intervention. We have provided further tips in Box 1, which might be helpful for researchers interested in undertaking similar adaptations of existing evidence-based interventions.

Overall, the use of a systematic process for adaptation allowed us to systematically track and pinpoint content areas that should remain the same as well as direct areas to be further customized and modified. Most importantly, it offered the research team
Adapting a fatigue intervention for patients with CML

Our results provide evidence that CML patients have a need for more information on their disease and treatment. As CML is transforming into a chronic illness, practitioners should be aware that it is important for patients to better understand their disease and the way their response is monitored. This might help patients in better understanding and adjusting to the long-term nature of their treatment. The Internet-assisted delivery channel of the intervention appears to be a suitable and flexible vehicle to disseminate information for CML patients while reducing travel burden. The pilot RCT will be useful to supplement the preliminary findings on acceptability of Internet-assisted intervention delivery reported in this study.

Our results set the stage for the pilot RCT (currently underway) that is evaluating the usability, feasibility and efficacy of the adapted CBT for targeted therapy-related fatigue. Ultimately, if proven effective, this will provide nurses and other health care professionals with important referral options to interventions offering practical and patient-tailored strategies to address the most important factor limiting quality of life of CML patients treated with TKIs. In summary, this work provides a strong foundation for addressing a major treatment consequence in the growing population of patients for whom targeted therapies are transforming cancer from a life threatening to a chronic illness.

Box 1. Tips for researchers interested in undertaking similar adaptations of an existing evidence-based intervention

Researchers might find the following tips helpful:

- Upon initiating a project, form a collaborative professional relationship with the original intervention developers and clinicians who have experience with delivering the intervention. Ask them to be part of the team.
- Adhere to systematic and iterative steps that guide the adaptation process driven by initial need for the intervention through the final testing of the adapted intervention. This provides an adaptation blueprint that endorses relevancy, rigor and meaning.
- Establish a multidisciplinary team (local, national or international) to ensure inclusion of varied perspectives and who bring content-specific knowledge, methodological, and theoretical expertise. This might include well-versed researchers with backgrounds in psychology, nursing, and education as well as providers who care for the patient group. Include a team member with experience in developing and/or adapting interventions or education programs.
- Engage key stakeholders such as patient and providers to make adaptations to ensure the ecological validity of the intervention, while still maintaining fidelity to the intervention’s core elements.
- Maintain a robust and consistent communication plan with study team members to ensure discussions and decisions about adaptation adjustments.
- Finally, carefully document processes and justify modifications of the intervention protocol to monitor success, and revisions of the adapted components.
REFERENCES


Adapting a fatigue intervention for patients with CML


Adapting a fatigue intervention for patients with CML
PART II

FATIGUE IN PATIENTS WITH INCURABLE DISEASE
CHAPTER 5

FATIGUE IN ADVANCED CANCER PATIENTS: CONGRUENCE BETWEEN PATIENTS AND THEIR INFORMAL CAREGIVERS ABOUT PATIENTS’ FATIGUE SEVERITY DURING CANCER TREATMENT WITH PALLIATIVE INTENT AND PREDICTORS OF AGREEMENT

Hanneke Poort, Marlies Peters, Marieke Gielissen, Stans Verhagen, Gijs Bleijdenberg, Winette van der Graaf, Alison Wearden, Hans Knoop

ABSTRACT

Background
Informal caregivers (ICs) are increasingly involved in the monitoring of symptoms during advanced cancer patients’ treatment with palliative intent. A common, but subjective symptom during this extended treatment phase is fatigue. This exploratory longitudinal study aimed to determine agreement between patients and ICs about patients’ fatigue severity. In addition, predictors of agreement over time were studied.

Methods
A sample of 107 advanced cancer patients (life expectancy ≥ six months) and their ICs completed the subscale fatigue severity of the Checklist Individual Strength based on the patient’s status at baseline and six months later. This 8-item subscale has a validated cut-off to determine the presence of clinically relevant levels of fatigue. ICs’ own fatigue severity, strain, self-esteem, and relationship satisfaction were examined as predictors of agreement.

Results
107 dyads completed measures at baseline, 69 dyads six months later. At baseline, ICs’ significantly overestimated patients’ fatigue severity ($p < .001$) with a moderate amount of bias (Cohen’s $d = 0.48$). In 81 of the 107 dyads (76%) there was congruence about the presence or absence of severe fatigue. On a group level, congruence did not significantly change over time. On a dyad level, there was a tendency to either remain congruent or reach congruence. Next to baseline congruence, ICs’ fatigue severity and strain predicted ICs’ in fatigue ratings ($R^2 = 0.23$).

Conclusion
The majority of ICs accurately predict presence or absence of clinically relevant levels of patients’ fatigue. ICs’ own fatigue severity and strain should be taken into account, as they influence agreement.
INTRODUCTION

A diagnosis of cancer, particularly when the disease is incurable, impacts not only the patient but also the informal caregiver (IC) [1]. ICs are faced with new responsibilities in medical, emotional, and practical domains [2]. The main aims of care for patients with incurable cancer are to prolong patients’ lives, while maintaining acceptable quality of life (QoL) by providing pain and symptom relief [3]. Due to advances in medical treatment, patients with certain types of incurable cancer receiving treatment with palliative intent may now live for an extended period [4, 5]. This extended phase of cancer treatment with palliative intent is associated with the occurrence of several physical and psychological symptoms. One of the most frequently reported symptoms is fatigue [6]. Fatigue is often cited as being among the most distressing symptoms [7-9] and has a negative impact on QoL, performance status, and daily activities [7, 10, 11]. Both patients and ICs have to deal with this distressing and disabling symptom [12].

Cancer-related fatigue (CRF) is defined by the NCCN as “a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” [13], which cannot be objectively measured. Patients directly perceive their fatigue, whereas ICs can only know about the patients’ fatigue indirectly, that is, from what the patient communicates verbally or non-verbally. It is important to understand ICs’ perceptions for several reasons. First, perceptions drive IC responses to patients’ fatigue, which in turn can have an impact on patients. For example, failing to perceive that the patient feels severely fatigued would prevent ICs from giving attention to this symptom, thereby potentially resulting in a perceived lack of social support by the patient. In turn, it is known that a perceived lack of social support can be a perpetuating factor of fatigue [14]. Second, ICs are increasingly involved in the care for advanced cancer patients. For example, monitoring and management of symptoms during palliative treatment may rely on information from ICs. It is therefore important to know whether an IC can give a meaningful additional rating of the severity of patients’ fatigue.

Studies focusing on patient and proxy-ratings typically assess physical and psychosocial symptoms by asking both patients and proxies to complete questionnaires based on the patients’ status. Findings of a review by Tang & McCorkle (2002) confirmed that ICs’ ratings of terminal cancer patients’ QoL agreed moderately well and when discrepancies existed, ICs held a more negative view of patients’ QoL than did patients [15]. However, agreement in fatigue ratings has not been studied extensively in incurable cancer patients receiving treatment with palliative intent. A cross-sectional study focusing on agreement in symptom ratings
by 52 advanced lung cancer patients and their ICs found that fatigue ratings were moderately correlated [16]. Yet, ICs rated patients’ fatigue significantly higher than did patients themselves. ICs’ perceived lack of social support, self-reported health, and caregiver self-esteem influenced agreement in various dimensions of symptoms. However, none of these three factors appeared to have an impact for agreement on fatigue. Another cross-sectional study, assessing agreement between 66 advanced cancer patients and their ICs found that agreement for lack of energy was poor to fair [17]. In addition, levels of disparity were correlated with IC characteristics (e.g. emotional state, caregiver burden) on several individual symptoms and on all symptom subscales of the Memorial Symptom Assessment Scale. However, these studies had a cross-sectional design and thus it is not possible to determine the pattern of agreement in fatigue ratings over time, nor temporal relationships between patients’ and ICs’ ratings of fatigue and other variables. Furthermore, no attempt was made to determine agreement on clinically relevant levels of fatigue, even though decisions about symptom management will often be based on the evaluation of whether fatigue is severe enough to be clinically relevant.

The present exploratory longitudinal study had three aims. First, we aimed to examine at the dyadic and group level whether ICs’ ratings of patients’ fatigue are congruent with patients’ ratings both when fatigue severity is measured continuously, and when the presence or absence of clinically relevant levels of fatigue is determined using a questionnaire with a validated cut-off for severe fatigue. Based on previous studies reporting poor agreement for more subjective symptoms [15, 18], we expected lack of agreement for ICs’ ratings of patients’ fatigue severity on a continuous level. However, we did not have hypotheses about the magnitude of this expected disagreement or about the agreement of ICs’ and patients’ ratings for clinically relevant levels of fatigue. Second, we studied the patterns of agreement over time to investigate whether agreement between ICs’ and patients’ perceptions changed over time. We had no specific hypothesis for this research question. Finally, predictors for the degree of agreement between ICs’ and patients’ fatigue severity ratings over time were explored. Based on the findings of previous studies [16, 17], we explored several characteristics associated with the IC (i.e. ICs’ fatigue severity, caregiver strain, and/or caregiver self-esteem) that could explain a significant amount of variance in ICs’ perceptions. For ICs with a partner relation to the patient, relationship satisfaction was added as a potential predictor since it has been suggested that this relates to closeness [19], i.e. sharing thoughts or feelings [20], and thus might influence the congruence between ICs’ and patients’ perceptions.
METHODS

Study population
The current study was part of a larger study examining fatigue in advanced cancer [21, 22]. Patients were recruited between December 2008 and June 2010 from two Dutch hospitals, the Radboud university medical center (Nijmegen) and the Jeroen Bosch Hospital (Den Bosch). Patients with advanced (i.e. incurable or metastatic) cancer who visited the department of medical oncology for cancer treatment with palliative intent with a life expectancy of at least six months were invited to participate in the study together with their IC. Potential patient participants were identified by the treating physician and telephoned by a researcher to explain study procedures. In addition, patients received written information. Eligible patients that gave consent were asked to identify their principal IC. ICs could either be the patients’ partner or have another relation to the patient (e.g. parent, daughter/son, or friend). Identified ICs were telephoned by a researcher to verify willingness to participate and also received written information. All patients and ICs gave oral informed consent. Paper versions of the questionnaires were sent to patients and ICs by mail in separate packages, which could be returned in a self-addressed, stamped envelope. ICs were explicitly instructed to complete the questionnaires apart from their patient-partners. Medical ethical committees of both hospitals approved the study.

Fatigue measurement
Fatigue severity in patients and ICs was assessed with the subscale fatigue severity of the Checklist Individual Strength (CIS-fatigue) [23]. Besides reporting their own fatigue, ICs also responded to a version of the CIS-fatigue adapted to elicit their perspective on the patients’ fatigue. ICs were instructed to focus on how their partner (or parent, daughter/son, or friend) had felt during the last two weeks. In addition, first-person item statements were changed into the third-person perspective (e.g. ‘My partner feels fatigued’). The CIS-fatigue consists of 8 items, scored on a 7-point Likert scale. Total scores range from 8 (no fatigue) to 56 (severe fatigue). The cut-off for severe fatigue is set at 35, i.e. two standard deviations (SD) above the mean of a healthy control group [23]. This cut-off has been used previously for assessing severe fatigue in cancer patients during or after curative cancer treatment [24-27] as well as in patients receiving cancer treatment with palliative intent [28]. The CIS-fatigue was administered at baseline (T0) and six months later (T1).

Patient and informal caregiver characteristics
At baseline, characteristics of the patients including demographic data (i.e. age and gender) and medical data (i.e. tumour type and treatment modality) were retrieved from medical records. In addition, ICs answered demographic questions (i.e. age, gender, and relation to the patient) at T0 and questionnaires about caregiver strain
and caregiver self-esteem at T0 and T1. The Caregiver Strain Index (CSI) contains 13 yes/no statements about perceived caregiver strain [29]. Total scores range from 0 to 13 and a score of 7 or more indicates high caregiver burden. Positive experience of caregiving was measured with the subscale self-esteem of the Caregiver Reaction Assessment-Dutch (CRA-D) [30]. The CRA-D self-esteem consists of 7 items scored on a 5-point Likert scale of 1-5. Total scores range from 7 to 35 and a higher score represents more caregiver self-esteem [31]. ICs with a partner relationship to the patient also completed a questionnaire about their relationship satisfaction. The subscale marital satisfaction of the Maudsley Marital Questionnaire (MMQ) [32] consists of 10 items scored on a 9-point Likert scale of 0-8. Total scores range from 0 (very satisfied) to 80 (very dissatisfied).

**Statistical analysis**

Only data from dyads where both members had completed the CIS-fatigue were included in the analyses. Due to the natural course of the illness, significant attrition was expected. No missing data were replaced. Analyses for T1 data only included dyads that completed the CIS-fatigue at both T0 and T1.

**ICs’ ratings of patients’ fatigue at baseline**

First, an intraclass correlation coefficient (ICC) [33] was calculated to examine congruence between patient and IC proxy ratings on the CIS-fatigue [34]. The strength of congruence as reflected by the ICC was labelled as follows: ≤ 0.40 poor to fair agreement; 0.41-0.60 moderate agreement; 0.61-0.80 good agreement; 0.81-1.00 excellent agreement [35]. Second, for each dyad, a continuous congruence score (CCS) was calculated by subtracting the patients’ CIS-fatigue score from the ICs’ CIS-fatigue proxy score, so that a positive CCS denoted the ICs’ proxy assessment of patients’ fatigue severity as being higher than that of the patient [36]. Given the possible range of 8 to 56 for scores on the CIS-fatigue, possible CCSs ranged between -48 and 48. In accordance with previous studies examining dyadic congruence, a minimal threshold for a clinically relevant CCS was set at >10% of the possible range [37, 38]. Therefore, CCSs exceeding 4.8 or -4.8 were considered clinically relevant. At the group level, additional paired samples t-tests were used to determine the mean CCS at baseline, being indicative of bias in ICs’ proxy score relative to those of the patient. The statistical magnitude of any observed bias was examined by calculating the effect size (Cohen’s d) using mean CCS and SD [39]. An effect size of at least 0.2 was considered small, 0.5 was considered moderate, and 0.8 was considered large [39, 40].

To examine absolute congruence, CIS-fatigue scores of patients and ICs’ CIS-fatigue proxy scores were dichotomized as denoting the presence (≥35) or absence (<35) of severe fatigue. Dyadic congruence about the presence or absence of severe
fatigue was determined and coded (0=congruence, 1=incongruence). At the group level, proportion agreement was calculated to evaluate the amount and direction of congruence between patients and ICs. Incongruent dyads were further classified as to whether the IC under- or over-estimated the presence of severe fatigue relative to the patient.

**ICs' ratings of patients' fatigue over time**

First, a paired samples $t$-test was used to test whether the means for CCS at T0 and T1 differed over time. Second, two separate Bland-Altman plots were drawn for agreement at T0 and T1 to visually inspect patterns of agreement over time [41, 42]. In this graphical method, the differences between patient and IC ratings (CCS) are plotted against the gold standard, i.e. patients' fatigue ratings [43]. The 95% limits of agreement were defined as the mean CCS ± 1.96 times the SD of the differences. Horizontal lines were drawn for the mean CCS and the upper and lower limits of agreement. We inspected width of the 95% limits of agreement, trends in agreement, and consistency of variability across the graph for T0 and T1. In addition, we calculated the proportion of dyads with a CCS exceeding the threshold for clinical relevance.

To examine absolute congruence over time, we calculated the numbers and percentages of dyads that were classified as congruent or incongruent about the presence or absence of severe fatigue at T0 and T1.

**Predictors of continuous congruence**

Bivariate correlations between baseline predictors and CCS at T0 and T1 were determined. Following the methods described by Snow et al. (2005), a multivariate hierarchical regression analysis was conducted to determine which IC characteristics at T0 significantly predicted CCSs at T1 [36]. Predictors were entered into the regression model in three blocks: (1) CCS at T0, (2) T0 predictors that significantly correlate with CCS at T1, (3) the remaining predictors. All data analyses were performed using Statistical Package for Social Science (SPSS; version 20) for Windows. The significance level was set at 0.05.

**RESULTS**

**Patients' and ICs' characteristics**

Of the 142 eligible dyads for the larger study, 131 agreed to participate and 107 completed the CIS-fatigue at T0, enabling inclusion in this study (75% response). Due to expected attrition, 69 of the 107 dyads filled out the CIS-fatigue at both time points (64% response). The most common reason for loss of dyads was because the patient
died during the study \((n=21)\), followed by patients that did not want to participate any further mostly because of disease deterioration \((n=14)\) or for unknown reasons \((n=4)\). The demographic and medical characteristics of the total group of 107 patients and ICs are presented in Table 1.

Table 1. Baseline characteristics \((n=107)\)

<table>
<thead>
<tr>
<th></th>
<th>Patients N (%)</th>
<th>Informal Caregivers N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (min-max)</td>
<td>59 (30-79)</td>
<td>60 (27-80)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>43 (40.2)</td>
<td>55 (51.4)</td>
</tr>
<tr>
<td>Female</td>
<td>64 (59.8)</td>
<td>52 (48.6)</td>
</tr>
<tr>
<td>Relation to patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partner</td>
<td>96 (89.7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>11 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Tumor type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>31 (29.0)</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>28 (26.2)</td>
<td></td>
</tr>
<tr>
<td>Urogenital</td>
<td>13 (12.1)</td>
<td></td>
</tr>
<tr>
<td>Bone and soft tissue</td>
<td>11 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Gynaecologic</td>
<td>10 (9.3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>14 (13.1)</td>
<td></td>
</tr>
<tr>
<td>Treatment modality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>55 (51.4)</td>
<td></td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>19 (17.8)</td>
<td></td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>13 (12.1)</td>
<td></td>
</tr>
<tr>
<td>Chemo + Targeted therapy</td>
<td>15 (14.0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (4.7)</td>
<td></td>
</tr>
</tbody>
</table>

ICs’ ratings of patients’ fatigue at baseline
At baseline, the intraclass correlation indicated excellent agreement between patient and IC proxy ratings \((ICC = 0.81)\). Patients’ mean CIS-fatigue scores and ICs’ mean CIS-fatigue proxy scores were 31.9 and 36.6, respectively. ICs’ CIS-fatigue proxy scores differed significantly from patients’ CIS-fatigue scores. ICs tended to overestimate the level of fatigue \((\text{mean difference } 4.74, \text{SD } 9.97, t: 4.917, p < .001)\). The effect size suggested that the amount of systematic bias was moderate \((\text{Cohen’s } d = 0.48)\). At the group level, the mean CCS for fatigue severity did not exceed the clinically relevant threshold \((i.e. 4.8 \text{ or } -4.8)\). The CCS for each dyad exceeded the clinically relevant threshold in 68 of the 107 dyads \((64\%)\).
When the cut-off for severe fatigue (i.e. ≥ 35) was applied, 81 of the 107 dyads (76%) were congruent about the presence (n=43) or absence (n=38) of severe fatigue in patients. Of the remaining 26 incongruent dyads, 22 ICs (85%) overestimated the presence of severe fatigue, while only 4 ICs (15%) underestimated the presence of severe fatigue.

**ICs’ ratings of patients’ fatigue over time**
The following results are related to the 69 dyads that completed the CIS-fatigue (patient and proxy-rating) at both T0 and T1. Dyads lost to follow-up (n=38) were not significantly different with respect to mean CCS at T0 compared to dyads that completed both assessments (n=69). In addition, ICs’ own fatigue severity, self-esteem, relationship satisfaction, and strain did not differ significantly at baseline (all p’s > 0.05).

The mean CCS for fatigue severity was lower at T1 (2.97, SD 10.28) compared to T0 (4.62, SD 10.54), though not significantly so (p > 0.05). **Figures 1A and 1B** depict Bland-Altman plots of the difference between patient and IC ratings of patients’ fatigue. For both time points, a wide range for the limits of agreement was found. No trends were observed and variability across the graph was consistent at both time points. The CCS for each dyad exceeded the clinically relevant threshold in 45 (65%) and in 48 (70%) of the 69 dyads at T0 and T1, respectively.

We calculated the numbers and percentages of dyads that were classified as congruent or incongruent about the presence or absence of severe fatigue at T0 and T1. Forty-two of the 51 dyads (82%) that were classified as congruent at T0 were also congruent at T1. However, 13 of the 18 dyads (72%) that were incongruent at T0 were in agreement about the presence or absence of severe fatigue at T1.

**Predictors of continuous congruence**
**Table 2** shows descriptives for patients’ fatigue and ICs’ own fatigue severity, strain, self-esteem, and relationship satisfaction at T0 and T1. All variables remained largely stable over time (p’s > 0.1). **Table 3** displays predictor-outcome correlations for T0 and T1. The CCS at T0, ICs’ own fatigue severity and strain correlated significantly with the CCS at T1 (p’s < 0.05).
Figure 1A. Bland-Altman plot for agreement at T0 ($n=69$)

Figure 1B. Bland-Altman plot for agreement at T1 ($n=69$)
Table 2. Descriptives of patient and caregiver variables for dyads who completed both T0 and T1

<table>
<thead>
<tr>
<th>Patient and caregiver variables</th>
<th>Descriptives T0 Mean</th>
<th>SD</th>
<th>N</th>
<th>Descriptives T1 Mean</th>
<th>SD</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient fatigue</td>
<td>30.68 13.32</td>
<td>69</td>
<td></td>
<td>31.71 14.50</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Caregiver fatigue proxy scores</td>
<td>35.30 14.08</td>
<td>69</td>
<td></td>
<td>34.68 16.16</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Caregiver fatigue</td>
<td>22.70 13.39</td>
<td>69</td>
<td></td>
<td>22.59 13.27</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Caregiver strain</td>
<td>2.87 1.86</td>
<td>68</td>
<td></td>
<td>2.87 2.06</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Caregiver self-esteem</td>
<td>26.38 3.78</td>
<td>66</td>
<td></td>
<td>25.78 4.25</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Caregiver relationship satisfaction</td>
<td>9.42 9.36</td>
<td>60</td>
<td></td>
<td>10.37 10.41</td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

Due to missing data total N is < 69. Only calculated for ICs with a partner relation to the patient.

Table 3. Predictor-CCS correlations for dyads who completed both T0 and T1

<table>
<thead>
<tr>
<th>Baseline predictor variables</th>
<th>Predictor-CCS T0 correlations</th>
<th>Predictor-CCS T1 correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P-value</td>
</tr>
<tr>
<td>CCS T0</td>
<td>1</td>
<td>n.a.</td>
</tr>
<tr>
<td>Caregiver fatigue</td>
<td>.335</td>
<td>.005*</td>
</tr>
<tr>
<td>Caregiver strain</td>
<td>.272</td>
<td>.025*</td>
</tr>
<tr>
<td>Caregiver self-esteem</td>
<td>-.319</td>
<td>.009*</td>
</tr>
<tr>
<td>Caregiver relationship satisfaction</td>
<td>.075</td>
<td>.571</td>
</tr>
</tbody>
</table>

* Statistically significant values (p < .05).
CCS = Continuous Congruence Score. Due to missing data total N is < 69. Only calculated for ICs with a partner relation to the patient.

Subsequently, three-block hierarchical regression was used. In block 1, the CCS at T0 was entered as a control variable. Block 2 predictors included those variables that significantly correlated with CCS at T1 (ICs’ own fatigue severity and strain). Remaining predictors in block 3 (self-esteem and relationship satisfaction) were entered based on previous research [16, 19]. The CCS at T0 predicted 13% of the variance in CCSs at T1. ICs’ own fatigue severity and strain accounted for an additional 10% of the variance in CCSs at T1. Block 3 variables did not account for significant additional variance. Thus, 22% of the variability in CCSs at six months was explained by the CCS at baseline, ICs’ own fatigue severity and strain (Table 4).
Table 4. Regression model to predict CCS T1

<table>
<thead>
<tr>
<th>Block 1</th>
<th>Unstandardized Coefficients</th>
<th>Model Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta</td>
<td>S.E.</td>
</tr>
<tr>
<td>CCS T0</td>
<td>.357</td>
<td>.125</td>
</tr>
<tr>
<td>Block 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCS T0</td>
<td>.247</td>
<td>.138</td>
</tr>
<tr>
<td>Caregiver fatigue</td>
<td>.138</td>
<td>.109</td>
</tr>
<tr>
<td>Caregiver strain</td>
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<td>.766</td>
</tr>
<tr>
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<tr>
<td>CCS T0</td>
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<tr>
<td>Caregiver fatigue</td>
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<td>Caregiver strain</td>
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<td>.788</td>
</tr>
<tr>
<td>Caregiver self-esteem</td>
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<td>.440</td>
</tr>
<tr>
<td>Caregiver relationship satisfaction</td>
<td>.161</td>
<td>.149</td>
</tr>
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</table>

* Statistically significant values (p < .05). CCS = Continuous Congruence Score.

DISCUSSION

The present exploratory longitudinal study was performed to determine congruence between patients and ICs about patients’ fatigue severity both on a continuous and clinically relevant level during cancer treatment with palliative intent in patients with a life expectancy of at least six months. In addition, we examined a number of possible predictors of agreement between ICs’ and patients’ ratings of patients’ fatigue. The results show that ICs rate patients’ mean fatigue severity significantly higher than patients themselves. This echoes with findings in other studies where, across diseases and symptoms, ICs tend to over report on more subjective patient symptoms and underestimate quality of life [44]. However, the overestimation effect in our study was only of moderate size and patient and IC ratings of patients’ fatigue on a continuous scale were highly correlated. When fatigue ratings were dichotomised around a cut-off of clinically significant fatigue, there was a greater degree of agreement. In the small proportion of incongruent dyads, overestimation was more likely to occur. No trend for a change in ratings of fatigue on a continuous scale over time was observed. When fatigue ratings were dichotomised, an overall tendency to either remain congruent or reach congruence over time existed.

We found that in addition to baseline congruence, several characteristics of the ICs also predicted congruence at six months. The fact that ICs’ own fatigue severity and strain were associated with less congruence could be due to a reporting bias, which in
itself could be related to negative affect on the part of the IC. That is, more strained ICs report higher levels of fatigue for themselves and for their patient partners, because both measures are confounded or inflated by negative affect. Mulligan et al. (2014) showed that negative affect is not only associated with reporting your own symptoms, which is already a well established finding, but also with reports of symptoms in others [45]. Contrary to our expectations, we did not find a relationship between caregiver self-esteem and relationship satisfaction and congruence. However, overall mean scores reflected a reasonable amount of caregiver self-esteem and high relationship satisfaction, which may have prevented us from finding significant results due to a restriction of range effect.

In the present study, it is hard to know what an IC is actually rating when they rate the patients’ fatigue. We do not know how ICs estimate how tired the patient feels. It would be interesting to explore whether they are for example relying on behavioural or verbal correlates of fatigue to make the judgement. McPherson and Addington-Hall (2004) analysed family members’ narratives and found that family members draw on different sources when evaluating advanced cancer patients’ pain, anxiety, and depression, such as contextual cues, expectations, behavioural referents, knowledge in general and knowledge of the patient [46]. Whether this also applies to estimating fatigue remains to be determined. Davis et al. (2007) used a think-aloud approach to study discordance in parent-proxy and child self-reported quality of life [47]. Application of this qualitative approach while ICs complete the fatigue questionnaire might be helpful in further unravelling this.

Measurement issues do not only play a role in the IC-proxy rating. Fatigue is a subjective symptom and we worked on the assumption that the patient’s experience is primary and that the patient’s expressed ratings are the most valid measures. Therefore, patients’ fatigue ratings were taken as the gold standard to which the IC-proxy rating was compared. Yet, patients’ ratings themselves might be affected by various factors. For example, a response shift may cause patients to continuously rate fatigue at the same level as previously, even though the IC can observe more fatigue-related behaviour (e.g. resting more). Alternatively, a qualitative study reported that advanced cancer patients admitted intentionally minimizing symptoms to prevent ICs from becoming distressed [48]. Thus, for consultations where important treatment decisions are to be made, a second rating of patients’ fatigue by an IC may provide physicians with a more complete reflection of patients’ fatigue and facilitate discussing how well patients are holding up with treatment.

The study has several limitations including the high attrition rate, which resulted in a rather small sample size for the longitudinal analyses. The main reason for attrition was because the patient died during the study. Although this might have led to a
selected group of relatively fit patients at T1, we did not find significant differences between dyads that completed the study and dropouts with respect to baseline CCS or IC characteristics. Next, the patient-IC relationship was quite homogeneous, with almost 90% having a partner relationship. This limits the possibility of generalizing our findings to ICs with a different relation to the patient. A further limitation is that we adapted the CIS for proxy use without validation of the adapted version. In addition, although we tried to secure non-contamination of questionnaires between patients and ICs, it is possible that ICs discussed questions or answers with patients. Moreover, we focused on IC characteristics as potential predictors for agreement but other factors, such as cognitive functioning, patients’ performance status, or presence of other symptoms, were not measured in this study and may also impact agreement. Also, cancer staging information was not recorded, though based on eligibility criteria only patients with a stage 3 or 4 cancer diagnosis were eligible. Information about performance status or time since diagnosis was not collected and would have been particularly useful in the context of our findings on the course of agreement over time. Finally, we analysed our data without multiple test adjustment following recommendations for exploratory studies by Bender & Lange (2001), thus significant results should be viewed as exploratory results [49]. Despite these limitations, to our knowledge this was the first exploratory study investigating ICs’ perceptions of patients’ fatigue with a longitudinal design, allowing to study the pattern of agreement over time and to explore temporal relationships between IC characteristics and agreement. Moreover, the current study used a cut-off point to determine clinically meaningful agreement about the presence or absence of severe fatigue, adding to studies that merely examined agreement on a continuous level.

In conclusion, ICs can accurately predict presence or absence of clinically relevant levels of severe fatigue in advanced cancer patients receiving treatment with palliative intent. However, on a continuous level ICs tend to overestimate patients’ fatigue. For ICs, this may trigger the feeling that they need to do more for the patient, which could lead to increased IC strain. We suggest that it would be useful to include measures of ICs’ ratings of patients’ fatigue when delivering extended care for advanced cancer patients. Agreement did not change significantly over time. It is however important to take into account ICs’ affective state when asking for judgments about patients’ fatigue in both research and clinical settings, as the response is likely to be affected if the IC is fatigued or feeling strained. The latter finding also seems to point to the need to attend to ICs’ own fatigue and burden in the context of caring for a patient with advanced, incurable cancer.
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CHAPTER 6

PSYCHOSOCIAL INTERVENTIONS FOR FATIGUE DURING CANCER TREATMENT WITH PALLIATIVE INTENT

Hanneke Poort, Marlies Peters, Gijs Bleijenberg, Marieke Gielissen, Martine Goedendorp, Paul Jacobsen, Stans Verhagen, Hans Knoop

In revision, Cochrane Database of Systematic Reviews
ABSTRACT

Background
Fatigue is a prevalent and burdensome symptom for patients with incurable cancer receiving cancer treatment with palliative intent and is associated with poorer quality of life. Psychosocial interventions seem promising for the management of fatigue among cancer patients.

Objectives
To assess the effects of psychosocial interventions for fatigue in adult patients with incurable cancer receiving cancer treatment with palliative intent.

Search methods
We searched the following databases: CENTRAL, MEDLINE, Embase, CINAHL, PsycINFO, seven clinical trial registries, and the reference lists of articles. The date of the most recent search was 29 November 2016.

Selection criteria
We included randomised controlled trials of psychosocial interventions in adults aged 18 years or over undergoing cancer treatment with palliative intent for incurable cancer compared with usual care or other control groups. Psychosocial interventions were defined as various kinds of interventions aiming to influence or change cognitions, emotions, behaviour, social interactions, or a combination of these. Psychosocial interventions of interest to this review had to involve at least two interactions between the patient and the care provider, in which the care provider gave the patient personal feedback concerning the changes they were trying to achieve. We included trials if they had fatigue as an outcome of interest.

Data collection and analysis
We used standard methodological procedures expected by Cochrane. Two authors independently considered trials for inclusion in the review, assessed risk of bias, and extracted data, including information on adverse events. We also assessed the evidence using GRADE (Grading of Recommendations Assessment, Development and Evaluation) and created a ‘Summary of findings’ table.

Main results
We identified 14 studies (16 reports) that met inclusion criteria for this review involving 3077 randomised participants in total. The majority of these studies had a mixed sample of participants and we obtained data for the subset of interest to this review (diagnosed with incurable cancer and receiving cancer treatment) from the study investigators of 12 studies. These 12 studies included in the subset meta-analysis for
Psychosocial interventions for fatigue during cancer treatment with palliative intent

fatigue post-intervention involved 535 participants. The studies investigated a broad range of psychosocial interventions with different intervention aims and durations. There were sources of potential bias, including a lack of description of the methods of blinding and allocation concealment and small size of the study populations.

Findings from our meta-analysis did not support the effectiveness of psychosocial interventions for reducing fatigue post-intervention (SMD -0.25, 95% CI -0.50 to 0.00; not significant; 535 participants, 12 studies; very low-quality evidence). First follow-up findings on fatigue suggested a benefit for participants assigned to the psychosocial intervention compared to the control group (SMD -0.66, 95% CI -1.00 to -0.32; 147 participants, 4 studies; very low-quality evidence), which was not sustained at second follow-up (SMD -0.41, 95% CI -1.12 to 0.30; not significant; very low-quality evidence).

Results for our secondary outcomes indicated very low-quality evidence for the efficacy of psychosocial interventions in improving physical functioning post-intervention (SMD 0.32, 95% CI 0.01 to 0.63; 307 participants, 7 studies). These findings were not sustained at first follow-up (SMD 0.37, 95% CI -0.20 to 0.94; not significant; 122 participants, 2 studies; very low-quality evidence). Findings did not support the effectiveness of psychosocial interventions for improving social functioning (MD 4.16, 95% CI 11.20 to 19.53; not significant; 141 participants, 4 studies), role functioning (MD 3.49, 95% CI -12.78 to 19.76; not significant; 143 participants, 4 studies), emotional functioning (SMD -0.11, 95% CI -0.56 to 0.35; not significant; 115 participants, 3 studies), or cognitive functioning (MD -2.23, 95% CI -12.52 to 8.06; not significant; 86 participants, 2 studies) post-intervention. Only three studies evaluated adverse events. These studies did not find a difference between the number of adverse events in participants from the intervention versus control group.

Using GRADE, we considered the overall quality of evidence for our primary and secondary outcomes to be very low. As such, we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of the effect. Limitations to study quality and imprecision due to sparse data resulted in downgrading of the quality of the data. Additionally, most studies were at high risk of bias due to their small sample size for the subset of patients with incurable cancer (fewer than 50 participants per arm) leading to uncertainty about effect estimates.

Authors’ conclusions
There is a lack of evidence around the benefits of psychosocial interventions to reduce fatigue in adult patients with incurable cancer receiving cancer treatment with palliative intent. Additional studies with larger samples are required to see if there is
a benefit of psychosocial interventions to address fatigue in patients with incurable cancer.

BACKGROUND

This review is partly based on suggested wording from the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS CRG).

Description of the condition

According to the World Health Organization, palliative care is “an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual” (WHO 2002). For a long time, cancer treatment with palliative intent for patients with incurable cancer was considered as the terminal phase, reflecting the last months or year before an expected death. However, due to advances in the medical treatment of cancer, more patients with incurable cancer receiving cancer treatment with palliative intent can now expect to be chronically ill for an extended period of years (Italiano 2008; Miller 2008). This leads to ambiguous medical prognoses: patients with incurable cancer may be sick enough to die, but could also live for many years (Lynn 2003). Nowadays, it is more common to distinguish three stages of cancer treatment with palliative intent (Wanrooij 2010). The first phase, disease palliation, has the aim of reducing disease activity to improve survival time and quality of life. The second phase, symptom palliation, primarily aims to prevent and treat symptoms to improve quality of life. The last phase, terminal palliation, focuses on quality of life and quality of dying. The current review will focus on patients with incurable cancer receiving cancer treatment aimed at disease palliation (phase 1) or receiving cancer treatment aimed at disease palliation combined with symptom palliation (phase 1 and 2). This implies that patients need to receive some form of cancer treatment.

Fatigue is one of the symptoms most commonly reported by patients receiving cancer treatment with palliative intent (Barnes 2002), with reported prevalence rates up to 99% (Butt 2008; Hauser 2008; Radbruch 2008; Stone 2008; Teunissen 2007). It is frequently cited as being among the most distressing symptoms (Butt 2008; Hofman 2007; Paiva 2013). Fatigue is associated with reduced quality of life, poor performance status, and difficulty in performing daily activities (Butt 2008; Hauser 2008; Tanaka 2002). Many factors are likely to contribute to fatigue in patients with incurable cancer receiving cancer treatment with palliative intent. Fatigue could result from the underlying disease itself, as well as the cancer treatments patients receive.
Psychosocial factors can also contribute to fatigue, e.g. sleeping problems and mood disturbances such as depression and anxiety (Peters 2014).

There are various ways to define and measure fatigue and there is no consensus about the definition of fatigue in cancer patients (Minton 2009; Minton 2013). Cancer-related fatigue (CRF) is a term that is most widely used to describe this symptom. The National Comprehensive Cancer Network (NCCN) defines CRF as “a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” (Mock 2000). A more simple distinction between a subjective lack of energy (symptom) or a confirmable decrease in strength over time (physical or muscular weakness) has also been used (Stone 1999). The most simplified operationalization of fatigue is to ask patients whether or not they feel fatigued or tired. We will use the NCCN definition of fatigue for this review. However, we will also include studies with tiredness, weakness, lack of energy or exhaustion as an outcome of interest. Although according to the NCCN guidelines fatigue should be measured by using self-report instruments with established cut-off scores (Mock 2000), studies measuring fatigue via other self-report instruments will also be included.

Efforts to manage fatigue during cancer treatment with palliative intent for patients with incurable cancer should first focus on identifying and treating somatic causes. Often, no specific somatic cause of fatigue can be identified other than the underlying disease itself or the cancer treatments patients receive. In these situations, the management of fatigue usually involves multiple strategies. These strategies can be divided into pharmacological and non-pharmacological interventions. Pharmacological interventions include stimulant drugs, corticosteroids, erythropoietic agents and antidepressants. A Cochrane review focusing on pharmacological interventions for fatigue concluded that no recommendation could be given for a specific drug treatment for fatigue in palliative care patients (Mücke 2015). Non-pharmacological interventions include both psychosocial interventions as well as physical activity. Psychosocial interventions are the focus of this review, and will be explained further below. The role of physical activity/exercise in the management of fatigue during and after cancer treatment is supported by evidence from a Cochrane review (Cramp 2012). However, it remains unclear whether exercise is also effective for patients receiving cancer treatment with palliative intent. Only a few included RCTs were focused on this particular patient group.

**Description of the intervention**

Psychosocial interventions seem promising for the management of fatigue among patients with incurable cancer. For this review, psychosocial interventions are defined
as various kinds of interventions aiming to influence or change cognitions, emotions, behaviour, social interactions, or a combination of these, in order to achieve better mental health and/or fewer problems, for example less fatigue. Such interventions may include cognitive behavioural therapy, coping skills training, motivational therapy, mindfulness-based stress reduction, and psycho-educational or educational therapies, which may be combined with mind-body elements such as yoga, relaxation breathing or progressive muscle relaxation. Psychosocial interventions of interest in this review involve systematic treatment with at least two interactions between the patient and the care provider, in which the care provider gives the patient personal feedback concerning the changes they are trying to achieve. Exercise interventions, often primarily aimed at increasing physical fitness or level of physical activity, will be excluded.

**How the intervention might work**

Although there are various interventions aimed at CRF that can be labelled as psychosocial, the majority draw techniques from cognitive therapies, behavioural therapies, and educational theories. Psychosocial interventions usually include a rationale or framework for therapy and collaborative goal setting (Peyrot 2007). Education about disease and the role of behaviour, beliefs, and emotions in disease and symptoms are common elements of therapy (Authier 1975). In addition, establishing a therapeutic alliance between a therapist and a patient is a key component of a psychosocial intervention (Frank 1990; Martin 2000; Orlinsky 2004), which consists of an emotional bond, agreement on goals, and active collaboration (Bordin 1979; Gaston 1990).

Generally, psychosocial interventions assume that thoughts, feelings, and actions are interconnected and can influence fatigue and its consequences. During the intervention, patients learn to change thoughts, actions or feelings in relation to symptoms. Psychosocial interventions differ in the assumptions made about the mechanisms responsible for the change in fatigue brought on by the intervention. The assumed mechanisms of change of each intervention are different, depending on the theoretical models underpinning them. Psychosocial interventions can use one or a combination of techniques or treatment methods to influence symptoms and their consequences (Peyrot 2007). An example of a mechanism for reducing fatigue is cognitive restructuring used in cognitive therapies (Beck 1970; Beck 1976) to change dysfunctional beliefs (e.g. catastrophising or feeling helpless with respect to fatigue) and encourage patients to develop more helpful beliefs (Beck 2011). This is thought to reduce symptoms or change negative emotional states which worsen symptoms like fatigue. Another possible mechanism for reducing fatigue is behaviour modification (Bandura 1969) to change behavioural responses to fatigue (e.g. resting when fatigued). Influencing these behavioural patterns by, for example, gradually increasing physical activity in patients, can be used to reduce symptoms and enhance patients’
self-efficacy (Bandura 1997). These are only examples of assumed mechanisms, and more potentially-effective techniques and treatment methods with their own specific therapeutic mechanisms responsible for the reduction in CRF are available, such as yoga or (psycho) educational therapies (see also the American Society of Clinical Oncology [ASCO] clinical practice guidelines; Bower 2014).

While research has provided empirical support for the efficacy of psychosocial interventions for fatigue irrespective of the presence of a medical condition, knowledge about the therapeutic mechanisms of these interventions is scarce. The limited work that has been done is primarily performed in the field of cognitive behaviour therapy (CBT) for patients with medically-unexplained fatigue (i.e. chronic fatigue syndrome [CFS]). Mediation analysis of CBT for CFS demonstrated that changes in both beliefs and behaviour can mediate the effects of CBT (Chalder 2015; Wiborg 2011; Wiborg 2012). Mediation analysis of CBT for patients with multiple sclerosis showed that the decrease in fatigue was explained by a change in beliefs about fatigue (Knoop 2012). The lack of knowledge about therapeutic mechanisms is even more evident for interventions reducing fatigue in patients with cancer. Although CBT was found to be effective for reducing post-cancer fatigue (Gielissen 2006) and is now recommended in the ASCO clinical practice guidelines for cancer-related fatigue (Bower 2014), the mechanisms of change are not known, but the effects on fatigue were not mediated by an increase in objective physical activity or fitness (Gielissen 2012; Prinsen 2013). To permit unequivocal conclusions to be drawn about the therapeutic mechanisms of psychosocial interventions that may produce a reduction in fatigue, further research is needed.

Why it is important to do this review
Advances in the medical treatment of patients with incurable cancer have led to prolonged survival. Maintaining quality of life is an important goal of cancer treatment with palliative intent. Fatigue is not only a prevalent symptom, but also a factor affecting patients’ quality of life. A previous Cochrane review (Goedendorp 2009) investigated the effectiveness of psychosocial interventions among adult cancer patients receiving cancer treatment. However, few RCTs in that review included only patients with incurable cancer receiving cancer treatment with palliative intent, and the review did not analyse the effectiveness of psychosocial interventions for fatigue in these patients separately. The current review will replace Goedendorp 2009. It will differ from the previous review by focusing exclusively on fatigue in patients with incurable cancer. Our current review will aid oncologists providing cancer treatment with palliative intent, to inform patients about evidence-based psychosocial interventions for fatigue.
OBJECTIVES

To assess the effects of psychosocial interventions for fatigue in adult patients with incurable cancer receiving cancer treatment with palliative intent.

METHODS

Criteria for considering studies for this review

Types of studies
We only included randomised controlled trials (RCTs). We required full journal publication, with the exception of online clinical trial results, summaries of otherwise unpublished clinical trials, and abstracts with sufficient data for analysis.

Types of participants
We included studies of adult patients (aged 18 years and above) with a diagnosis of incurable (advanced or metastatic) cancer. We included studies in which participants received some form of disease-focused treatment, such as chemotherapy, hormonal therapy, targeted therapy, immunotherapy, surgery, and/or radiation therapy. For studies with a mixed sample of participants with either curable and incurable cancer and/or either receiving cancer treatment or not receiving cancer treatment, we only included those participants with incurable cancer and receiving cancer treatment. We contacted the authors with a request for data or results where separate information on cancer diagnosis and/or treatment was not reported in the study. If separate data for the subset of participants of interest to this review could not be provided or authors did not respond after two reminders, we only included the study if it reported 80% or more having incurable cancer and receiving cancer treatment. We excluded studies in which patients received terminal care (i.e. hospice or end-of-life care).

Types of interventions
We included studies with a broad range of psychosocial interventions compared to usual care or control conditions (not being a psychosocial intervention). These interventions included psychotherapy, psycho-education, or support groups, and interventions including elements such as cognitive restructuring, changing coping strategies, self-help or self-care, relaxation, energy conservation, or stress management. The psychosocial interventions could be given individually or in groups, and by care providers from different professions such as psychologists or nurses. We only included psychosocial interventions involving a systematic treatment with at least two contacts between the patient and the care provider, in which personal feedback concerning the changes the patient was trying to achieve was given. For example, in the first session a care provider might advise a patient to change their coping behaviour aiming to reduce fatigue, whilst discussing
the progress of the patient and giving feedback on the patient’s behaviour in following sessions. We excluded studies in which interventions were exclusively aimed at exercise.

**Types of outcome measures**

Studies used a variety of outcome measures. Included studies had fatigue, tiredness, weakness, lack of energy, lack of vitality, or exhaustion as an outcome of interest. Fatigue could be assessed by specific validated fatigue questionnaires with multiple items or by other self-report methods. Examples of the latter are one or more items on fatigue as part of a quality of life instrument, a Numerical Rating Scale (NRS), a Visual Analogue Scale (VAS) assessing fatigue, or assessment of fatigue as part of a symptom list and scored as ‘present’ or ‘absent’. Secondary outcomes included physical, social, role, emotional, and cognitive functioning assessed by a suitable instrument such as the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) or the Short Form Health Survey.

We measured adverse events of psychosocial interventions as absent or present. We provided a narrative description of these effects. In addition, we analysed measures of function when used as an outcome measure in studies.

**Primary outcomes**

1. Fatigue post-intervention (alternative terms: tiredness, weakness, lack of energy, lack of vitality, or exhaustion).

**Secondary outcomes**

1. Fatigue (first and second follow-up);
2. Physical functioning (post-intervention and at first and second follow-up);
3. Social functioning (post-intervention);
4. Role functioning (post-intervention);
5. Emotional functioning (post-intervention);
6. Cognitive functioning (post-intervention);
7. Adverse events of psychosocial interventions (post-intervention).

**Search methods for identification of studies**

**Electronic searches**

We searched the following databases without language or date restrictions:

- The Cochrane Central Register of Controlled Trials (CENTRAL) (via CRSO) searched 29/11/16;
- MEDLINE (via Ovid) 1946 to Nov week 3 2016;
- Embase (via Ovid) 1974 to 2016 Nov 29;
- CINAHL (via EBSCOhost) 1982 to November 2016;
- PsycINFO (via Ovid) 1806 to November week 3 2016.
We used Medical Subject Headings (MeSH) or equivalent and text word terms. We exploded MeSH terms where appropriate. Where appropriate we applied the Cochrane filter for the identification of RCTs, as published in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). The search strategies can be found in Appendix 2-6.

**Searching other resources**

We searched the metaRegister of controlled trials (mRCT) (http://www.controlled-trials.com/mrct), clinicaltrials.gov (http://www.clinicaltrials.gov), the WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/), the Australian New Zealand Trials Registry (http://www.anzctr.org.au/), the ISRCTN register (http://www.isrctn.com/), the UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/), and the Netherlands Trial Register (http://www.trialregister.nl/trialreg/index.asp) with the keywords ‘cancer’ and ‘fatigue’ to identify additional completed or ongoing studies. In addition, we checked relevant reviews and reference lists of retrieved articles for additional studies, and we performed citation searches on key articles. Where necessary, we contacted authors for additional information.

**Data collection and analysis**

**Selection of studies**

Two review authors (HP, MP) independently determined eligibility by reading the abstract of each study identified by the search. These two authors independently eliminated studies that clearly did not satisfy inclusion criteria, and obtained full copies of the remaining studies. The same two authors read these studies independently to select relevant studies, and in the event of disagreement, a third author adjudicated (HK). We did not anonymise the studies before assessment. We included a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart which shows the status of identified studies (Moher 2009), as recommended in Part 2, Section 11.2.1 of the Cochrane Handbook (Higgins 2011).

**Data extraction and management**

Two review authors (HP, MP) independently extracted data using a standard form and checked for agreement before entry into Review Manager (RevMan 2014). We included information about:

**Participant characteristics**

- Demographic characteristics such as age and gender;
- Disease characteristics such as cancer diagnosis and cancer treatment;
- Inclusion/exclusion criteria for participation in study.
Psychosocial intervention characteristics
We extracted the following information for each study arm:
- Nature, type of delivery, and content of the intervention and control condition;
- Time point of delivery of intervention in relation to cancer treatment (during or after);
- Duration of the intervention and total number of sessions;
- Description and number of intervention providers;
- Duration and nature of training and supervision given to the intervention providers;
- Participant adherence and contamination;
- Intervention provider treatment integrity and existence of treatment protocol.

Methods and outcomes
- Random sequence generation;
- Allocation concealment;
- Incomplete outcome data (amount, nature and handling of missing data);
- Size of the study and power calculation;
- Blinding of outcome assessors;
- Quality of the control condition;
- Equality of treatment expectations;
- Therapist and/or researcher allegiance;
- Key outcomes and measurement instruments used to assess fatigue;
- Adverse events of the psychosocial intervention;
- Timing, frequency and duration of follow-up for each outcome;

We collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. We collected characteristics of the included studies in sufficient detail to populate the ‘Characteristics of included studies’ table. A study authored and co-authored by five of the review authors was included in the ‘Characteristics of ongoing studies’ table.

Assessment of risk of bias in included studies
Two authors (HP, MP) independently assessed risk of bias for each study, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) and adapted from those used by the Cochrane Pregnancy and Childbirth Group. We resolved any disagreements by discussion. We completed a ‘Risk of bias’ table for each included study using the ‘Risk of bias’ tool in RevMan (RevMan 2014).
We assessed the following for each study:

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator) or unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number).

- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes) or unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (e.g. open list).

- Blinding of outcome assessment (checking for detection bias). This is usually assessed based on the methods used to blind study participants and personnel from knowledge of which intervention a participant received. However, in RCTs investigating the effects of psychosocial interventions, it is impossible to blind the care providers to the intervention they are giving to patients. It is also nearly impossible to blind the patients to the intervention to which they were assigned. We judged risk of bias in blinding of outcome assessment on whether the measures were administered and collected by an assessor who was blind to the treatment allocation. We assessed the methods as: low risk of bias (study states that outcome assessment was blinded and describes the method used to achieve blinding); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how it was achieved); or high risk of bias (studies in which outcome assessors were not blinded).

- Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk (< 10% of participants did not complete the study or > 10% with sensitivity analysis or mixed model analysis); unclear risk of bias (used ‘last or baseline observation carried forward’ analysis, as progression in terms of fatigue is not unexpected in advanced cancer patients with missing outcome data); or high risk of bias (used ‘completer’ analysis or post-intervention t-test).

- Selective reporting (checking for possible reporting bias). We assessed studies as being at low risk of bias (all the data fully reported in the study); unclear risk of bias (data not fully reported in the study, but authors responded to data requests); or high risk of bias (data not fully reported in the study and authors did not respond to data requests).
· Size of the study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (≥ 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); or high risk of bias (< 50 participants per treatment arm).

· Yates 2005 developed a quality rating scale designed to measure the quality of RCTs for psychological interventions. Based on their recommendations, we included two further items to assess (1) the quality of the control condition and the efforts made to ensure that as many features as possible have been controlled for (adequate, partial, inadequate); and (2) equality of treatment expectations (adequate, inadequate). Furthermore, when reported, we noted the allegiance of the therapist and/or researcher to a particular psychosocial intervention (see ‘Characteristics of included studies’ table) to take an allegiance effect into account (Berman 1985; Wampold 2001; Dragioti 2015).

**Measures of treatment effect**
We evaluated fatigue outcomes at both post-intervention and follow-up assessments using RevMan (RevMan 2014). We calculated the mean difference and 95% confidence interval (CI) for continuous data. If not reported, we planned to calculate standard deviations using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We standardized mean differences of assessment tools measuring fatigue in different ways in order to combine results across tools and used mean differences otherwise. We planned to calculate the relative risks (RRs) and 95% CI where dichotomous data were reported (i.e. studies measuring fatigue as present or absent). We planned to report the proportion of participants experiencing any adverse events of psychosocial interventions, and combine studies using RR (and 95% CI).

**Unit of analysis issues**
One study had more than two intervention arms (Johansson 2008). It was decided that, the three arms which had relevant interventions for the aim of this review would be combined into one intervention group. We planned to report intra-cluster correlations and undertake adjustment where necessary for any identified randomised cluster trials.

**Dealing with missing data**
We analysed data for all participants in the group to which they were randomised, regardless of whether or not they received the allocated treatment. We did not exclude trials on the basis of missing data. In the Discussion section we address the potential impact of missing data on the findings of the review.
**Assessment of heterogeneity**
We assessed clinical diversity by documenting the participant characteristics represented in each study, focusing on factors such as age, gender, study eligibility criteria, cancer diagnosis and cancer treatment. Furthermore, we documented heterogeneity in psychosocial interventions, such as duration, delivery, profession of the care providers, and nature of the control condition. In addition, we assessed diversity in ways of measuring fatigue and timing of fatigue assessment.

**Assessment of reporting biases**
We assessed the possibility that publication bias affected this review as a whole using a funnel plot.

**Data synthesis**
Two authors (HP, MP) independently assessed heterogeneity by visual inspection of the forest plot, and based on the quantitative results of both the $X^2$ and the $I^2$ statistic. We performed meta-analysis for clinically homogeneous studies according to the inverse-variance method for continuous outcomes. We planned to use fixed-effect models, but since the patient populations were quite variable in cancer diagnosis and treatment (as were the interventions), we employed random-effects models. We expressed results as standardised mean differences (SMDs) or mean differences (MDs) for continuous outcomes. For any dichotomous outcomes, we would have expressed results as risk ratios (RR) using the Mantel-Haenszel method. We used Review Manager software for analysis (RevMan 2014). We presented a narrative synthesis for studies for which required data were unavailable for meta-analysis.

**Quality of the evidence**
Two review authors (HP, MP) independently rated the quality of each outcome. We used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system to rank the quality of the evidence using the GRADEprofiler Guideline Development Tool software (GRADEpro 2015), and the guidelines provided in Chapter 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The GRADE system uses the following criteria for assigning grade of evidence:
- High: we are very confident that the true effect lies close to that of the estimate of the effect;
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
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- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We decreased the grade rating by one (-1) or two (-2) if we identified:
- Serious (-1) or very serious (-2) limitation to study quality;
- Important inconsistency (-1);
- Some (-1) or major (-2) uncertainty about directness;
- Imprecise or sparse data (-1);
- High probability of reporting bias (-1).

### ‘Summary of findings’ table

We included a ‘Summary of findings’ table to present the main findings in a transparent and simple tabular format. In particular, we included key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the outcomes of fatigue, physical functioning, social functioning, role functioning, emotional functioning, cognitive functioning, and adverse events of psychosocial interventions.

### Subgroup analysis and investigation of heterogeneity

Where sufficient data were available, we planned to undertake subgroup analysis for the primary outcome based on aspects of the intervention that may influence its effectiveness: duration (short versus intermediate-long), intervention delivery (group versus individual, psychologist versus other profession), intervention type (mono versus multidisciplinary), and aim of the intervention (aimed at decreasing fatigue versus other). We did not perform subgroup analysis for the intervention deliverer (psychologist versus other profession), as insufficient data were available. In addition, we planned to perform subgroup analysis for type of assessment tool (continuous versus dichotomous) and for studies in which some level of fatigue was an eligibility criterion for patient participation versus those in which it was not. Due to insufficient data available, we were unable to perform these subgroup analyses. Given the low number of studies with a low overall risk of bias (i.e. an estimated low risk of bias in all domains of the ‘Risk of bias’ assessment) we did not use subgroup analysis based on overall risk of bias. We performed post-hoc subgroup analyses based on the provision of additional sessions between post-intervention and first and second follow-up assessments of fatigue (no additional sessions versus booster sessions).

### Sensitivity analysis

We performed post-hoc sensitivity analyses based on the number of participants per treatment arm at post-intervention and follow-up assessments, excluding those studies with fewer than 10 participants per treatment arm.
Figure 1. Study flow diagram

2874 records identified through database searching

1916 records after duplicates removed

1916 records screened

1741 records excluded

4 records unable to retrieve full-text

171 full-text articles assessed for eligibility

132 full-text articles excluded

23 full-text articles excluded with reasons (21 studies)

14 studies included in qualitative synthesis (across 16 reports)

12 studies included in quantitative synthesis (meta-analysis)
RESULTS

Description of studies
Key characteristics of the included studies are summarized below and in the Characteristics of included studies table. The excluded studies with potential relevance to this review are listed with reasons for their exclusion in the Characteristics of excluded studies table.

Results of the search
Our search identified 1909 unique citations after duplicates were removed through database searching. An additional seven citations were identified through conference abstracts or other references. After initial screening of the 1916 titles and abstracts for relevance to the review we retained 171 citations. We were unable to retrieve full-texts for four citations and excluded a further 132 citations that, based on the full text, and in some cases correspondence with original study investigators, did not meet the eligibility criteria. We excluded 21 studies (23 reports) with reasons. Therefore, there were 14 studies (16 reports) that met the inclusion criteria and were included in the review. For a further description of our screening process, see the study flow diagram Figure 1.

Included studies
Design
All 14 included studies were RCTs. In 13 studies the unit of randomisation was the individual participant (Armes 2007; Barsevick 2004; Barsevick 2010; Bordeleau 2003; Bruera 2013; Chan 2011; Classen 2001; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Steel 2016; Walker 2014). In one study the unit of randomisation was a group of 20 participants, with 10 being randomised to each condition (Edelman 1999).

Setting
Six studies were conducted in the United States of America (Barsevick 2004; Barsevick 2010; Bruera 2013; Classen 2001; Spiegel 1981; Steel 2016), three in the UK (Armes 2007; Sharpe 2014; Walker 2014), two in Canada (Bordeleau 2003; Savard 2006), one in Australia (Edelman 1999), one in Hong Kong (Chan 2011), and one in Sweden (Johansson 2008). The primary settings were university-affiliated hospitals in five studies (Bordeleau 2003; Classen 2001; Spiegel 1981; Johansson 2008; Savard 2006), cancer centres in seven studies (Armes 2007; Bruera 2013; Barsevick 2004; Barsevick 2010; Sharpe 2014; Steel 2016; Walker 2014), and a public hospital in two studies (Chan 2011; Edelman 1999).
Cancer diagnosis
In this review, we were interested in the effects of psychosocial interventions in participants diagnosed with incurable cancer. In six studies, all participants were diagnosed with incurable cancer (Bruera 2013; Bordeleau 2003; Classen 2001; Edelman 1999; Savard 2006; Spiegel 1981). Five of those studies included patients with metastatic breast cancer (Bordeleau 2003; Classen 2001; Edelman 1999; Savard 2006; Spiegel 1981), the other study included patients with any diagnosis of advanced cancer (Bruera 2013). The eight remaining studies had a mixed sample of participants diagnosed with incurable and potentially curable cancer (Armes 2007; Barsevick 2004; Barsevick 2010; Chan 2011; Johansson 2008; Sharpe 2014; Steel 2016; Walker 2014). The original study investigators of those eight studies were able to provide data for their subset of participants with incurable cancer and were thus included in the review.

Cancer treatment
In this review, we were interested in the effects of psychosocial interventions in participants receiving cancer treatment. In five studies, all participants were receiving cancer treatment during the intervention (Armes 2007; Barsevick 2004; Barsevick 2010; Chan 2011; Classen 2001). In seven studies, not all participants were receiving cancer treatment (Bordeleau 2003; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Steel 2016; Walker 2014). However, the original study investigators of those studies were able to extract data for their subset of participants receiving cancer treatment and thus these studies were included in the review. In the remaining two studies, it was unclear or unknown whether all participants were receiving cancer treatment (Bruera 2013; Edelman 1999). Clarification was sought from the original study investigators. Bruera 2013 confirmed that all participants were receiving cancer treatment. Edelman 1999 did not collect data on who was receiving treatment at the time of study participation. Yet, we believe it is likely that participants were receiving at least some form of cancer treatment during the intervention given the study population of patients with metastatic breast cancer. Therefore, both studies were included in the review.

Participants
The total sample sizes for the included studies ranged from 45 (Savard 2006) to 500 randomised participants (Sharpe 2014). However, as noted before, not all participants were diagnosed with incurable cancer and/or receiving cancer treatment. As a result, the sample sizes for the subset of participants of interest to this review were much smaller ranging from 15 (Walker 2014) to 110 evaluable participants (Chan 2011) at post-intervention assessment. Information on age and gender distribution was available for the total samples of the included studies, but not for the subset of interest to our review. The participants’ mean age for the total sample ranged from 50 years.
(Edelman 1999) to 64 years (Walker 2014). No information on the age distribution was reported in Chan 2011, but these data were provided upon request. Nine studies included both men and women (Armes 2007; Barsevick 2004; Barsevick 2010; Bruera 2013; Chan 2011; Johansson 2008; Sharpe 2014; Steel 2016; Walker 2014), with the proportion of males in the total sample ranging from 10% (Sharpe 2014) to 83% (Chan 2011). Four studies targeted only women (Bordeleau 2003; Classen 2001; Savard 2006; Spiegel 1981). Edelman 1999 did not provide any information on the gender distribution of the participants. We believe it is likely that only women were included given the study population of patients with metastatic breast cancer. Finally, it is important to note that Sharpe 2014 and Walker 2014 recruited only patients with a diagnosis of major depression comorbid with cancer.

Content of the intervention
A detailed description of the interventions delivered is provided in the Characteristics of included studies table. The interventions from 10 studies fell into one of three categories: cognitive behavioural therapies ($n=5$; Armes 2007; Savard 2006; Edelman 1999; Johansson 2008; Steel 2016), supportive-expressive group therapies ($n=3$; Bordeleau 2003; Classen 2001; Spiegel 1981), and energy conservation approaches combined with either activity management or sleep modification techniques ($n=2$; Barsevick 2004; Barsevick 2010). Four interventions did not fall within these categories. In Bruera 2013 the intervention included psychosocial support and education combined with either methylphenidate or placebo. The intervention in Sharpe 2014 and Walker 2014 included antidepressant medication in combination with problem-solving therapy and behavioural activation. Chan 2011 examined the effects of a psycho educational intervention consisting of education and relaxation. It was unclear whether the intervention protocol used in this study included some kind of personal feedback. Clarification was sought from the original study investigators, who confirmed that participants received personal feedback.

Nature of the intervention
The purpose of the interventions varied. Six studies investigated interventions specifically aimed to address fatigue (Armes 2007; Barsevick 2004; Barsevick 2010; Bruera 2013; Chan 2011; Steel 2016). In addition to fatigue, the intervention of Steel 2016 also aimed to reduce depression and pain. The intervention of Chan 2011 also aimed to reduce anxiety and breathlessness in addition to fatigue. Two of the six studies required some level of fatigue as an eligibility criterion for patient participation (Armes 2007; Bruera 2013). In the remaining eight studies, the intervention was aimed at mood disturbances and/or psychological benefit (Classen 2001; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Walker 2014), quality of life (Bordeleau 2003), or survival benefit (Edelman 1999).
Duration of the intervention
The total intervention duration varied between studies and ranged from short (two to three weeks) in four studies (Bruera 2013; Barsevick 2004; Barsevick 2010; Chan 2011) to long (12 months) in three studies (Bordeleau 2003; Classen 2001; Spiegel 1981). In the remaining seven studies, the intervention was given over a period of two to eight months and these were classified as having an intermediate duration (Armes 2007; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Steel 2016; Walker 2014). In the study by Steel 2016, the total intervention duration was not clearly stated but it is likely that the intervention was given over a period of six months after which the post-intervention assessment took place. In four studies, interventions consisted of an initial more intense intervention delivery during the first two (Edelman 1999; Savard 2006) or four months (Sharpe 2014; Walker 2014), followed by additional sessions (if needed) for a further period ranging from nine weeks (Savard 2006) to eight months (Sharpe 2014).

Providers
The intervention was delivered by nurses in four studies (Barsevick 2004; Barsevick 2010; Bruera 2013; Chan 2011) and by a combination of therapists (i.e. two or more psychologists, psychiatrists, counselors, and/or social workers) in five studies (Bordeleau 2003; Classen 2001; Edelman 1999; Spiegel 1981; Savard 2006). In one study, psychologists, physiotherapists, and nurses delivered the interventions (Johansson 2008). In two studies, interventions were delivered by non-clinicians, i.e. a research fellow (Armes 2007) or master’s level/PhD therapists (Steel 2016). Finally, a team consisting of a nurse, psychiatrist and the participant’s primary care physicians delivered the interventions in Sharpe 2014 and Walker 2014.

Delivery of the intervention
The psychosocial interventions were delivered using different approaches. In six studies interventions were delivered individually, either face-to-face (Armes 2007; Chan 2011; Savard 2006) or by telephone (Barsevick 2004; Barsevick 2010; Bruera 2013). Four studies used blended methods for intervention delivery consisting of individual face-to-face and telephone contacts (Johansson 2008; Sharpe 2014; Steel 2016; Walker 2014). In addition to these delivery channels, Johansson 2008 also used face-to-face group-based interventions and Steel 2016 also used a web-based platform. In four studies interventions were delivered in groups (Bordeleau 2003; Classen 2001; Edelman 1999; Spiegel 1981).
Training and supervision
Ten studies (Armes 2007; Barsevick 2004; Barsevick 2010; Bordeleau 2003; Bruera 2013; Chan 2011; Sharpe 2014; Spiegel 1981; Steel 2016; Walker 2014) reported that providers of the intervention were trained. The remaining four studies did not report whether providers were trained before delivering the intervention (Classen 2001; Edelman 1999; Johansson 2008; Savard 2006). Supervision of intervention delivery was reported in 11 studies (Armes 2007; Barsevick 2004; Barsevick 2010; Bordeleau 2003; Bruera 2013; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Steel 2016; Walker 2014). Three studies did not report whether intervention delivery was supervised (Chan 2011; Classen 2001; Edelman 1999).

Control condition
Nine studies compared the effects of a psychosocial intervention to usual care. In eight of those studies the usual care was no intervention (Armes 2007; Chan 2011; Edelman 1999; Johansson 2008; Sharpe 2014; Spiegel 1981; Steel 2016; Walker 2014), the other study assigned participants to a wait list condition (Savard 2006). In three studies, the intervention effects were compared to an attentional control group (Barsevick 2004; Barsevick 2010; Bruera 2013). In Classen 2001, participants in the control conditions were provided with a self-directed educational intervention, but the education materials were also provided to participants randomised to the intervention condition. In Bordeleau 2003, all participants received educational materials about breast cancer and its treatment, relaxation, and nutrition.

Outcome measures
Fatigue
All 14 included studies reported fatigue either as a primary, secondary or tertiary outcome. Ten studies used one instrument to measure fatigue (Chan 2011; Classen 2001; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Steel 2016; Walker 2014). The remaining four studies used two or more instruments (Armes 2007; Barsevick 2004; Barsevick 2010; Bruera 2013). Five of the 14 studies used the fatigue subscale of the Profiles of Mood States (POMS) (Barsevick 2004; Barsevick 2010; Classen 2001; Edelman 1999; Spiegel 1981). Another five studies used the fatigue scale of the EORTC QLQ-C30 (Armes 2007; Bordeleau 2003; Johansson 2008; Sharpe 2014; Walker 2014). The four remaining studies used other instruments to evaluate fatigue: Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale (Bruera 2013); Revised Piper Fatigue Scale, subscale intensity (Chan 2011); Multidisciplinary Fatigue Inventory (Savard 2006); and Functional Assessment of Cancer Treatment (FACT) Fatigue (Steel 2016). The four studies evaluating fatigue with more than one instrument used the following additional instruments: Visual Analogue Scale (VAS) of global fatigue (Armes 2007); Schwartz Cancer Fatigue Scale (Barsevick 2004); General Fatigue Scale (Barsevick 2004; Barsevick 2010); and the
subscale fatigue of the Edmonton Symptom Assessment Scale (ESAS) (Bruera 2013). Except for the single-item VAS of global fatigue used in the study of Armes 2007, all instruments are comprised of multiple items to measure fatigue.

**Physical, social, role, emotional and cognitive functioning**

Several measures of function were used in a number of the studies. Eight studies assessed physical functioning (Armes 2007; Barsevick 2010; Bordeleau 2003; Chan 2011; Johansson 2008; Savard 2006; Sharpe 2014; Walker 2014). Six of those eight studies used the physical functioning scale of the EORTC-QLQ-C30 and the other two studies used the physical component of the Short-Form Health Survey (SF-12 and SF-36). Social and role functioning was assessed in four studies (Bordeleau 2003; Johansson 2008; Sharpe 2014; Walker 2014) using the scales of the EORTC QLQ-C30. Emotional functioning was assessed in three studies using either the scale of the EORTC QLQ-C30 (Bordeleau 2003; Johansson 2008) or the mental component of the SF-12 (Barsevick 2010). Cognitive functioning was assessed in two studies using the scale of the EORTC QLQ-C30 (Bordeleau 2003; Johansson 2008). Two studies used other measures to evaluate functioning. Barsevick 2004 used a total score for the Functional Performance Inventory, a 65-item scale consisting of six subscales, including body care, household maintenance, physical exercise, recreation, spiritual activities, and social activities. In addition to the physical and mental component summary scores of the SF-12, Barsevick 2010 also used the interference items from the Brief Pain Inventory adapted to apply to symptoms rather than pain only (SXINT) and the Eastern Cooperative Oncology Group Performance Status.

**Adverse events**

Only three studies assessed adverse events of the intervention and reported the number of adverse events for the total sample (Bruera 2013; Sharpe 2014; Walker 2014). Bruera 2013 recorded the number of Grade ≥ 3 adverse events. Sharpe 2014 and Walker 2014 defined adverse events as deaths from any cause, admission to a psychiatric ward, or attempted suicide. In addition, Chan 2011 reported that the sole reason for drop out of participants was due to deaths.

**Post-intervention outcome assessments**

As a result of variance in intervention duration, the time between baseline and post-intervention outcome evaluation ranged from two weeks in Bruera 2013, eight weeks in Savard 2006, 26 weeks in Steel 2016, to 12 months in Bordeleau 2003, Classen 2001 and Spiegel 1981. Two studies reported on the post-intervention assessment, but the number of weeks or months between pre- and post-intervention assessment were not clearly described (Barsevick 2004; Edelman 1999). In Armes 2007, the intervention consisted of 3 sessions coinciding with administration of chemotherapy, but the total length of chemotherapy in number of days or weeks was not mentioned.
Outcomes were assessed at the end of chemotherapy (T1), 4 weeks after the end of chemotherapy (T2), and 9 months after recruitment to the study (T3). Although the original study investigators indicated that T2 was identified as the main outcome for the study, we used T1 as this was the first post-intervention assessment. In the study of Barsevick 2010, post-intervention assessment was performed at Days 43-46 or 57-60 depending on the type of cancer treatment participants received. The intervention in Sharpe 2014 was given over a 4-month period and then continued for a further eight months. The primary endpoint for the study was the 24-weeks assessment. Walker 2014 examined the same type of intervention as Sharpe 2014 in a group of participants with a poor prognosis cancer. Given this poor prognosis, the intervention continued for a further four months instead of eight months. In this study, Walker 2014 averaged fatigue data over the participant’s time in the study (up to a maximum of 32 weeks) into a single fatigue score, but these averaged fatigue scores were not available for meta-analysis. Therefore, we used the fatigue data collected at 24-week assessment in line with Sharpe 2014. Johansson 2008 randomised participants to one of four study arms and assessments took place three, six, 12 and 24 months after randomisation. Participants from the three intervention arms in this study were combined into one intervention group for the aim of this review. However, the three interventions had different durations and start-points after randomisation. We selected the six-month assessment as post-intervention assessment for our meta-analysis.

Follow-up outcome assessments
Eight studies included one (Barsevick 2004) or two follow-up assessments in the trial (Armes 2007; Chan 2011; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Walker 2014). However, four of these studies (Edelman 1999; Savard 2006; Sharpe 2014; Walker 2014) provided more than one additional session (if needed) in the follow-up period. Therefore, these studies were excluded from the primary meta-analyses for follow-up effects and included in subgroup analyses. The four remaining studies (Armes 2007; Barsevick 2004; Chan 2011; Johansson 2008) had different follow-up durations. First follow-up durations ranged from 3 weeks (Chan 2011) to 6 months (Johansson 2008) after post-intervention assessment. Second follow-up administration varied between studies and ranged from 9 weeks (Chan 2011) to 18 months (Johansson 2008) after post-intervention assessment.

Excluded studies
Of the 155 excluded full-texts in our review, only 21 studies (23 reports) had potential relevance to our study aim. We have listed the details regarding these 21 studies that we excluded in the Characteristics of excluded studies table.
**Ongoing studies**
We identified two studies that have not been completed (Poort; Serfaty). The characteristics of these studies are listed in the Characteristics of ongoing studies table.

**Risk of bias in included studies**
We assessed the risk of bias using the Cochrane ‘Risk of bias’ tool (Figure 2 and Figure 3) (Higgins 2011).

**Allocation (selection bias)**
**Random sequence generation**
Eight studies adequately described the method used to generate the random sequence and so we judged them to be at low risk of bias for this domain (Armes 2007; Classen 2001; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Steel 2016; Walker 2014). Five studies did not specify the method of randomisation (Barsevick 2004; Barsevick 2010; Bordeleau 2003; Bruera 2013; Spiegel 1981) and we judged them to be at unclear risk of bias. In addition, Chan 2011 used a ‘lucky draw method’ but no description was reported, therefore this study was also judged as having an unclear risk of bias. We did not identify any studies at high risk of bias for this domain.

**Allocation concealment**
Six studies fully described how the allocation of the sequence was concealed and we judged them to be at low risk of bias for this domain (Armes 2007; Bordeleau 2003; Johansson 2008; Sharpe 2014; Steel 2016; Walker 2014). Eight studies did not adequately describe how the allocation of the sequence was concealed and we judged them to be at unclear risk of bias (Barsevick 2004; Barsevick 2010; Bruera 2013; Chan 2011; Classen 2001; Edelman 1999; Savard 2006; Spiegel 1981). We did not identify any studies at high risk of bias for this domain.

**Blinding (performance bias and detection bias)**
Five studies explicitly stated that the outcome assessors were masked to allocation and we judged them to be at low risk of bias for this domain (Chan 2011; Savard 2006; Sharpe 2014; Steel 2016; Walker 2014). No mention of blinding of outcome assessors or researchers was made in the nine other studies and we judged them to be at unclear risk of bias (Armes 2007; Barsevick 2004; Barsevick 2010; Bordeleau 2003; Bruera 2013; Classen 2001; Edelman 1999; Johansson 2008; Spiegel 1981). We did not identify any studies at high risk of bias for this domain.
Figure 2. Risk of bias graph: review authors’ judgments about each risk of bias item presented as percentages across all included studies

Figure 3. Risk of bias summary: review authors’ judgments about each risk of bias item for each included study
Incomplete outcome data (attrition bias)

Eight studies either had less than 10% missing data in the original study sample or more than 10% missing data but used adequate statistical analysis and as such we judged them to be at low risk of bias for this domain (Armes 2007; Barsevick 2004; Barsevick 2010; Bordeleau 2003; Chan 2011; Sharpe 2014; Steel 2016; Walker 2014). Three studies had more than 10% missing data and only included patients with at least one observation post-randomisation in the mixed model or slopes analysis and we judged them to be at unclear risk of bias (Classen 2001; Savard 2006; Spiegel 1981). The remaining three studies had more than 10% missing data and based on their adopted method of analysis we judged them to be at high risk of bias (Bruera 2013; Edelman 1999; Johansson 2008). Of note, these judgements were all based on the original study samples, since information on attrition for the subset of interest to this review was not available.

Selective reporting (reporting bias)

Thirteen studies adequately reported fatigue outcomes for the original study sample and we judged them to be at low risk of bias for this domain (Armes 2007; Barsevick 2004; Barsevick 2010; Bordeleau 2003; Bruera 2013; Chan 2011; Classen 2001; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Walker 2014). In Steel 2016, the authors performed two separate analyses but presented data of one analysis only (i.e. for the subgroup of patients reporting clinically significant symptoms at baseline). However, the original study investigators provided data for the total group on request and thus this study was judged to be at unclear instead of high risk of bias. We did not identify any studies at high risk of bias for this domain. Visual inspection of the funnel plot did not suggest publication bias.

Other potential sources of bias

Size of study

Information on the total sample size is provided because these were used in a few analyses. Based on the total sample sizes, four studies had fewer than 50 participants per treatment arm and we judged them to be at high risk of bias for this domain (Armes 2007; Bruera 2013; Savard 2006; Spiegel 1981). Nine studies had between 50 and 199 participants per treatment arm and we judged them to be at unclear risk of bias (Barsevick 2004; Barsevick 2010; Bordeleau 2003; Chan 2011; Classen 2001; Edelman 1999; Johansson 2008; Steel 2016; Walker 2014). We identified one study with more than 200 participants per treatment arm and we judged this study to be at low risk of bias (Sharpe 2014). However, the sample sizes for the subset of patients with incurable cancer included in the meta-analysis were much smaller. In fact, eight studies included in the subset meta-analysis would be judged to be at high risk of bias for this domain based on having fewer than 50 participants per treatment arm at baseline (Armes 2007; Barsevick 2004; Barsevick 2010; Edelman 1999; Johansson
2008; Savard 2006; Sharpe 2014; Walker 2014). The four remaining studies had between 50 and 199 participants per treatment arm and would therefore be judged to be at unclear risk of bias (Bordeleau 2003; Chan 2011; Classen 2001; Steel 2016).

Quality of the control condition
We judged the quality of the control condition to be adequate in three studies (Barsevick 2004; Barsevick 2010; Bruera 2013). In Barsevick 2004 and Barsevick 2010, the purpose of the control conditions was to control for the amount of time and attention received by the intervention groups. In Bruera 2013, participants in the control condition also received (non-therapeutic) phone calls. Four studies were judged to have partially controlled features of the control group (Bordeleau 2003; Chan 2011; Classen 2001; Steel 2016). We judged the efforts made to ensure that as many features as possible have been controlled for in the control group to be inadequate in seven studies (Armes 2007; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Walker 2014).

Equality of treatment expectations
Three studies were judged to have adequate equality of treatment expectations between intervention and control groups (Bruera 2013; Barsevick 2004; Barsevick 2010). These three studies compared the effects of the intervention to an attentional control group. The remaining 11 studies were judged to have inadequate treatment expectations (Armes 2007; Bordeleau 2003; Chan 2011; Classen 2001; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Steel 2016; Walker 2014).

Allegiance of the therapist
None of the studies reported the allegiance of the therapist and/or researcher. Two studies (Bordeleau 2003; Classen 2001) were conducted to replicate the findings of previous research about the effects of supportive-expressive group therapy (SEGT). Thus, we assumed that the investigators had at least some allegiance to SEGT.

Effects of interventions
See: Summary of findings table.
In this review, we were interested in the effects of psychosocial interventions compared to usual care or control conditions (not being a psychosocial intervention) in participants with incurable cancer receiving cancer treatment with palliative intent. As mentioned earlier, several studies had a mixed sample of participants with incurable and potentially curable cancer and/or receiving and not receiving cancer treatment during the psychosocial intervention. The analyses described in the following sections are subset meta-analyses, including only those participants of interest to our review.
Twelve of the 14 included studies were able to provide fatigue data for meta-analysis on the subset of interest to this review involving 535 participants in total at post-intervention assessment (Armes 2007; Barsevick 2004; Barsevick 2010; Chan 2011; Classen 2001; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Steel 2016; Walker 2014). With respect to measures of physical, social, role, emotional, and cognitive functioning, we received data from two to seven studies depending on the specific domain of functioning. Although Bordeleau 2003 could not provide fatigue data, they were able to provide data for all five domains of functioning. Data for adverse events were not available for the subset of interest to our review, but a narrative description on adverse events in the total sample has been provided further along this section.

As we were pooling data from heterogeneous populations and interventions, we used random-effects instead of fixed-effects models. Overall, we judged the quality of evidence for psychosocial interventions to be low. We downgraded the quality of evidence by two levels for risk of bias and imprecision.

**Fatigue**

Subset meta-analysis did not suggest a post-intervention outcome benefit for the psychosocial intervention group compared to the control group on the fatigue outcome measured with different instruments (SMD -0.25, 95% CI -0.50 to 0.00, P = 0.05; participants = 535; studies = 12; I² = 43%; Analysis 1.1; Figure 4). We found very low-quality evidence to suggest a benefit of psychosocial interventions for the secondary outcome fatigue at first follow-up (SMD -0.66, 95% CI -1.00 to -0.32, P = 0.0001; participants = 147; studies = 4; I² = 0%; Analysis 1.2; Figure 5). Psychosocial interventions did not influence secondary fatigue outcomes at second follow-up (SMD -0.41, 95% CI -1.12 to 0.30, P = 0.26; participants = 91; studies = 2; I² = 29%; Analysis 1.3; Figure 6).

**Non meta-analysed data**

Investigators of two included studies responded to our data request, but were unable to provide separate fatigue outcome data for meta-analysis. Bruera 2013 had a homogeneous sample of participants with incurable cancer receiving cancer treatment and found no statistically significant differences in the median improvement of FACIT Fatigue scores (P = 0.27) or ESAS Fatigue scores (P = 0.14) between intervention and control group. Bordeleau 2003 had a homogeneous sample of participants with incurable cancer, but not all participants were receiving cancer treatment. This study found a significant across-time deterioration in EORTC QLQ-C30 Fatigue scores (P = 0.003) using a mixed model for repeated measures. However, this deterioration did not differ between study arms and therefore this study also could not demonstrate a significant intervention effect.
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**Physical functioning**

We found very low-quality evidence to suggest a post-intervention outcome benefit of psychosocial interventions for physical functioning measured with different instruments (SMD 0.32, 95% CI 0.01 to 0.63, P = 0.04; participants = 307; studies = 7; I² = 35%; Analysis 2.1). Psychosocial interventions were not associated with a statistically significant improvement in physical functioning at first follow-up (SMD 0.37, 95% CI -0.20 to 0.94, P = 0.21; participants = 122; studies = 2; I² = 36%; Analysis 2.2).
Non meta-analysed data
Armes 2007 provided raw values instead of transformed scores for physical functioning and these could not be used for meta-analysis. This study had a mixed-stage sample of participants receiving cancer treatment for incurable and potentially curable cancer. The study investigators used a random-slope/random-intercept mixed model and reported a significant improvement in physical functioning for the original study population (coefficient 10, 95% CI 2.5 to 17.5, P = .009). However, we cannot conclude whether this improvement also applies to the small subset of participants with incurable cancer.

Social functioning
We saw no effect of psychosocial interventions on post-intervention social functioning measured with the scale of the EORTC-QLQ-C30 (MD 4.16, 95% CI -11.20 to 19.53, P = 0.60; participants = 141; studies = 4; I^2 = 55%; Analysis 3.1).

Role functioning
Psychosocial interventions did not influence post-intervention role functioning measured with the scale of the EORTC QLQ-C30 (MD 3.49, 95% CI -12.78 to 19.76, P = 0.67; participants = 143; studies = 4; I^2 = 52%; Analysis 4.1).

Emotional functioning
Psychosocial interventions did not influence post-intervention emotional functioning measured with different instruments (SMD -0.11, 95% CI -0.56 to 0.35, P = 0.65; participants = 115; studies = 3; I^2 = 23%; Analysis 5.1).

Cognitive functioning
There was no overall effect of psychosocial interventions on post-intervention cognitive functioning measured with the scale of the EORTC QLQ-C30 (MD -2.23, 95% CI -12.52 to 8.06, P = 0.67; participants = 86; studies = 2; I^2 = 23%; Analysis 6.1).

Adverse events
Data on adverse events were only available for the total study samples of three studies (Bruera 2013; Sharpe 2014; Walker 2014). Bruera 2013 had a homogeneous sample of participants with incurable cancer receiving cancer treatment and reported that the number of Grade ≥ 3 adverse events was similar between the methyphenidate and placebo arms, which were combined with a nursing or control intervention. Sharpe 2014 had a mixed-stage sample of participants with incurable and potentially curable cancer either receiving or not receiving cancer treatment. This study reported 34 cancer-related deaths (7%) during the trial (10 in the intervention group and 15 in the usual care group), one admission to a psychiatric ward (intervention group), and one attempted suicide (intervention group) for the total sample. None of these
events were judged by the study investigators to be related to the trial treatments or procedures. Walker 2014 had a mixed-stage sample of participants with incurable and potentially curable cancer either receiving or not receiving cancer treatment. This study reported 43 cancer-related deaths (30%) during the trial for the total sample (21 in the intervention group and 22 in the usual care group). No other serious adverse events occurred.

**Subgroup analyses**

**Intervention duration: short versus intermediate-long**
Three studies (participants = 163) were classified as having short intervention durations (two to three weeks; Barsevick 2004; Barsevick 2010; Chan 2011). The remaining nine studies (participants = 372) had intermediate (two to eight months) or long (12 months) intervention durations (Armes 2007; Classen 2001; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Steel 2016; Walker 2014). Meta-analysis to examine post-intervention results for these subgroups did not demonstrate a subgroup difference (Chi² = 0.21, P = 0.65; participants = 535; studies = 12; I² = 0%; Analysis 7.1).

**Intervention delivery: individual versus group**
Three studies (participants = 195) delivered interventions in groups (Classen 2001; Edelman 1999; Spiegel 1981). Eight studies (participants = 312) had interventions delivered individually (Armes 2007; Barsevick 2004; Barsevick 2010; Chan 2011; Savard 2006; Sharpe 2014; Steel 2016; Walker 2014). One study (Johansson 2008) had interventions that were either delivered individually or in groups, we did not include this study in the subgroup analysis. We did not find evidence supporting a subgroup difference (Chi² = 0.14, P = 0.70; participants = 507; studies = 11; I² = 0%; Analysis 7.2).

**Intervention type: mono versus multidisciplinary**
Nine studies (participants = 452) had interventions delivered by professionals from a single discipline (Armes 2007; Barsevick 2004; Barsevick 2010; Chan 2011; Classen 2001; Edelman 1999; Savard 2006; Spiegel 1981; Steel 2016). Three studies (participants = 83) had interventions delivered by professionals from two or more disciplines (Johansson 2008; Sharpe 2014; Walker 2014). We did not find evidence supporting a subgroup difference (Chi² = 0.20, P = 0.66; participants = 535; studies = 12; I² = 0%; Analysis 7.3).

**Intervention aim: fatigue specific versus other aim**
Five studies (participants = 232) providing fatigue outcome data for meta-analysis investigated the effects of a psychosocial intervention aimed at fatigue (Armes 2007; Barsevick 2004; Barsevick 2010; Chan 2011; Steel 2016). The remaining seven studies
(participants = 303) had different intervention aims (Classen 2001; Edelman 1999; Johansson 2008; Savard 2014; Sharpe 2014; Spiegel 1981; Walker 2014). We did not find evidence supporting a subgroup difference (\( \chi^2 = 1.08, P = 0.30; \) participants = 535; studies = 12; \( I^2 = 7.5\% \); Analysis 7.4).

**Additional sessions: no additional sessions versus booster sessions**

Four studies (participants = 147) had no additional sessions between post-intervention and first follow-up assessment and were thus included in the primary meta-analysis for fatigue at first follow-up (Armes 2007; Barsevick 2004; Chan 2011; Johansson 2008; Analysis 1.2). An additional four studies provided booster sessions between post-intervention and first follow-up assessment (Edelman 1999; Sarvad 2006; Sharpe 2014; Walker 2014). Three of those studies provided data for first follow-up (Edelman 1999; Sharpe 2014; Walker 2014). We did not find evidence supporting a subgroup difference (\( \chi^2 = 0.61, P = 0.44; \) participants = 270; studies = 7; \( I^2 = 0\% \); Analysis 7.5). Two studies (participants = 91) had no additional sessions between post-intervention and second follow-up assessment and were included in the primary meta-analysis for fatigue at second follow-up (Armes 2007; Chan 2011; Analysis 1.3). Three studies provided data for second follow-up but included booster sessions (Edelman 1999; Sharpe 2014; Walker 2014). We did not find evidence supporting a subgroup difference (\( \chi^2 = 0.18, P = 0.67; \) participants = 202; studies = 5; \( I^2 = 0\% \); Analysis 7.6).

**Sensitivity analysis**

Three of the 12 studies with fatigue outcomes that featured in the post-intervention meta-analysis had fewer than 10 participants per treatment arm post-intervention (Armes 2007; Johansson 2008; Walker 2014). We performed a sensitivity analysis, removing data from these three studies. This analysis also did not suggest a post-intervention outcome benefit for the psychosocial intervention group compared to the control group (SMD = -0.30, 95% CI -0.59 to 0.00, \( P = 0.05; \) participants = 476; studies = 9; \( I^2 = 56\% \); Analysis 8.1). At first and second follow-up only one included study had at least 10 participants per treatment arm (Chan 2011). Sensitivity analyses demonstrated that the findings of this study (participants = 153) were in accordance with the results of the primary meta-analysis at first follow-up (SMD = -0.70, 95% CI -1.10 to -0.30, \( P = 0.0005; \) Analysis 8.2) and second follow-up (SMD = -0.23, 95% CI -0.67 to 0.22; \( P = 0.32; \) Analysis 8.3).
DISCUSSION

Summary of main results
This review identified 14 studies for inclusion, with a wide range of patient samples and psychosocial interventions. Twelve of the 14 studies were able to provide data on fatigue for our subset meta-analysis involving 535 participants post-intervention. There was a lack of clear evidence to either support or not support the use of psychosocial interventions for reducing fatigue in patients with incurable cancer during cancer treatment. Seven of the 14 studies provided data on physical functioning involving 307 participants post-intervention. Psychosocial interventions may improve physical functioning post-intervention or reduce fatigue at first follow-up, or both. However, most subsets of data were too small to be reliable and only a limited number of studies with a limited number of participants contributed to the follow-up findings. Four of the 14 studies provided data on social and role functioning, three studies on emotional functioning, and two studies on cognitive functioning. We did not find evidence to either support or not support the use of psychosocial interventions for improving these domains of functioning post-intervention. In addition, there was a broad range of interventions and follow-up durations across studies with considerable attrition between assessments. Data on adverse events were sparse. Only three studies that included pharmacological interventions in addition to psychosocial interventions (Bruera 2013; Sharpe 2014; Walker 2014) reported on adverse events and found no difference in the number of adverse events between the intervention and control groups.

Overall completeness and applicability of evidence
We searched widely for evidence using five databases with no restriction of language and using search terms to help identify as wide a range of psychosocial interventions as possible. We found some important gaps in the evidence.

The main limitation of the review comes from the relative lack of data in this field. Six studies consisted of a homogenous sample of patients with incurable cancer. The remaining eight studies were comprised of a mixed sample of potentially curable and incurable patients. As a result, interventions from these eight studies were not specifically tailored to patients with incurable cancer. Yet, tailoring of psychosocial interventions could be important in achieving intervention effects, especially given the major difference in prognosis of patients with incurable cancer compared to patients with potentially curable cancer. Although investigators from these mixed-sample studies were able to provide data for the subset of incurable cancer patients, the sample sizes of these subsets were quite small. This is likely to result in a lack of power to detect treatment effects that may arise from the psychosocial interventions. In addition, our meta-analysis including means instead of individual patient data for the subsets of the total randomised study population is limited in that we were unable
to adjust for potential confounding factors. For these reasons, the results of the meta-analyses must be interpreted with caution.

We identified a limited number of studies (six) investigating interventions specifically aimed to address fatigue. However, only two of these six studies reported that the presence of some level of fatigue was an entry criterion for trial participation. This may lead to floor effects, restricting the potential range of fatigue scores and resulting in less room for improvement. Furthermore, a specific feature of the data available from the identified studies was the heterogeneity of intervention and follow-up durations. In addition, only four of the twelve studies contributed to the findings on follow-up effects. Three additional studies provided data for follow-up assessments, but interventions in these studies continued between post-intervention and follow-up assessments. Therefore, these three studies were excluded from the primary follow-up analysis and included in subgroup analyses that did not find a significant effect. Among the four studies that were included in the primary analysis for follow-up effects, there was considerable attrition between post-intervention and first follow-up assessment (attrition rate 18.5%). Although specific information on the reasons for attrition for the subset of interest to this review was not available, the attrition is unlikely to be random. In fact, it may be possible that attrition was associated with deterioration of health or death of the participant. This has implications for interpretation of the follow-up findings and thus these results should be interpreted with caution.

Overall, studies were predominantly comprised of female participants. This limits the ability to generalize research findings to male patients. Also, among the six studies that consisted of a homogeneous sample of patients with incurable cancer, only one study investigated intervention effects for a population other than metastatic breast cancer (Bruea 2013). Finally, in two studies (Sharpe 2014; Walker 2014), the investigated population was diagnosed with a major depressive disorder comorbid with cancer. Fatigue outcomes in these participants may have been associated with this depression, making it difficult to distinguish fatigue as a symptom of depression from cancer-related fatigue.

Quality of the evidence
We evaluated overall quality of the evidence using GRADE (see: Summary of findings table). We downgraded the GRADE quality of the evidence for all outcomes to very low because of unclear risk of selection bias and imprecision due to sparse data. We have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of the effect.
Potential biases in the review process
The review was conducted in keeping with the principles of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). It comprised electronic database searches and manual follow-ups for further references to maximise recall. None of the authors of this review were involved in any of the excluded or included studies. All studies were independently assessed for inclusion by two review authors, so we are confident that we have attempted to reduce bias in the review process. However, as with all systematic reviews and meta-analyses, subjective judgement is involved at various stages in the review process, from identifying studies to data extraction and analysis. As a result, although the search strategies, data extraction and analyses were thorough, there is a possibility of missing relevant studies and data.

Agreements and disagreements with other studies or reviews
In the Cochrane review by Goedendorp 2009 (co-authored by review authors GB, MFG, and SV), which did not include a meta-analysis, it was noted that there is limited evidence for the effectiveness of psychosocial interventions during cancer treatment in reducing fatigue. No distinction was made between the effectiveness of psychosocial interventions for patients receiving cancer treatment with curative or palliative intent. In our meta-analysis, we did not find clear evidence supporting the effectiveness of a range of psychosocial interventions on fatigue outcomes among the subset of incurable cancer patients. In addition, Goedendorp 2009 concluded that psychosocial interventions designed specifically to alleviate fatigue are promising intervention types for patients during cancer treatment. In our meta-analysis, there was no indication that interventions specifically aimed at reducing fatigue had more potential than interventions with a different aim for patients with incurable cancer receiving cancer treatment with palliative intent. This review highlights the current lack of evidence for psychosocial interventions reducing fatigue in patients with incurable cancer receiving treatment with palliative intent. The optimal approach to psychosocial interventions for fatigued patients with incurable cancer and the true extent of potential benefits and harms remain uncertain.

AUTHORS’ CONCLUSIONS

Implications for practice
This review found insufficient evidence for the effectiveness of psychosocial interventions to treat fatigue in patients with incurable cancer receiving treatment with palliative intent. Therefore, specific implications for patients with incurable cancer, for clinicians, for policy makers, or for funders of the interventions cannot be given.
Implications for research

Evidence
Further evidence is needed from high quality trials with large samples that fully report methodological characteristics and potential harms. Two ongoing studies were identified and aim to enrol 240 participants (Serfaty) and 219 participants (Poort) with a diagnosis of incurable cancer. Both studies with large samples have the potential to substantially aid answering of the research question of this review.

Population
More studies with a homogeneous study sample of patients with incurable cancer are needed. Targeting those patients most in need (i.e. those reporting clinically significant levels of fatigue) to eliminate potential floor effects has been recommended before (Bower 2014) and would be a helpful approach in future studies. Also, future studies should expand the focus beyond patients with metastatic breast cancer, as it is unknown whether findings from this patient group generalize to patients with other cancer diagnoses. Therefore, enriching the evidence with studies focusing on patients diagnosed with other types of incurable cancer would be helpful. Moreover, future studies should also include a substantial proportion of male participants and determine whether gender moderates treatment outcomes, as the majority of participants in the studies conducted thus far were females. Finally, given the difficulty of recruiting large enough samples in palliative care trials, multicentre studies are recommended, as studies with larger patient samples may be able to detect small but clinically relevant differences. Alternatively, application of novel research designs (e.g. replicated n-of-1 trials) might also be a worthwhile approach given the difficulties in conducting RCTs in patients receiving cancer treatment with palliative intent.

Intervention
Psychosocial interventions are part of a broader portfolio of available interventions for cancer-related fatigue, also including interventions focused on physical activity and pharmacological approaches. For future research aimed at psychosocial interventions, we recommend that protocols for a trial, including a detailed description of the intervention and its components, should be published or otherwise made publicly available. Also, tailoring the content of interventions to patients with incurable cancer would be helpful, given the substantial difference in prognosis between patients with potentially curable and incurable cancer. This difference has implications for the psychosocial factors thought to maintain fatigue and addressed by the interventions. Moreover, we would recommend short interventions delivered over a period of several weeks or months, with follow-up assessments following shortly (within 3-8 months) after intervention delivery. This is not only recommended with the aim to prevent participant attrition as much as possible, which complicates the interpretation of findings, but also to minimize the burden of participation.
Comparison
Given the current state of the evidence, we recommend that researchers conducting future trials compare psychosocial interventions to usual care or attentional control groups.

Outcome
There is no consensus on which instrument should be used to measure fatigue and reducing the variance in the outcome instruments used to measure the reduction in fatigue would be helpful. Also, future studies should clearly assess benefits and potential adverse events (e.g. increased psychological distress) of the intervention.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW
The final review differs from the protocol in four ways. First, we originally intended to select only those participants diagnosed with incurable cancer and receiving some form of active cancer treatment. However, several original study investigators of mixed sample studies did not respond to our request for subset data or were unable to select the subset of those participants. In those instances, we included studies when the sample involved > 80% of participants with incurable cancer and receiving some form of active cancer treatment. Second, we planned using fixed-effect models in all meta-analyses in this review. However, the patient populations were quite variable in cancer diagnosis and treatment (as were the interventions) and thus we employed random-effects models. Third, we originally used the overall term 'measures of function' in our protocol to reflect physical, social, role, emotional, and cognitive functioning as secondary outcomes of this review. In the final review, we have defined this outcome more clearly and changed our wording to all five individual domains instead of using an overall term. Last, we did not include different time points for outcomes in the protocol. Yet, some studies not only reported outcomes for post-intervention assessment but also for one or two follow-up assessments. We aimed to be as complete as possible in reporting our findings and thus also included fatigue and physical functioning data for first and second follow-up as secondary outcomes.
CHARACTERISTICS OF INCLUDED STUDIES

Armes 2007

<table>
<thead>
<tr>
<th>Methods</th>
<th>Design: RCT. Duration of study participation: 36 weeks.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>UK, Guys and St. Thomas’ Hospital NHS Trust and Bromley Hospitals NHS Trust. 60 patients (aged 59.1 years, 60% female) receiving chemotherapy and reporting significant fatigue.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Intervention group: brief, cancer-related fatigue-specific, behaviourally oriented intervention consisting of cognitive, behavioural, and general components. Control group: standard care. Cancer-related fatigue was not assessed routinely and the provision of advice regarding its management was delivered in an ad hoc manner.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>VAS Fatigue, EORTC QLQ-C30 Fatigue, and EORTC QLQ-C30 Physical functioning. Adverse events were not described.</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding: Cancer Research UK Nursing Research Training Fellowship (CP1052/0101 and C1428/A180).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>Originally, minimization as the method of treatment allocation. After the first 10 patients, simple random, permuted, block randomisation implemented.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Low risk</td>
<td>Statistician (unconnected to the study) generated randomisation, provided a central telephone service for patient allocation, and kept a copy of the randomisation codes.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Unclear risk</td>
<td>Questionnaires either posted or given to patients in the chemotherapy clinic by first study author. Insufficient information to permit judgment of low or high risk.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>More than 10% missing data, but data analysed using t tests and random-slope/random-intercept mixed models using a generalized linear latent and mixed model.</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Low risk</td>
<td>All the data are fully reported in the study.</td>
</tr>
<tr>
<td>Size of the study</td>
<td>High risk</td>
<td>Fewer than 50 participants randomised per treatment arm at baseline.</td>
</tr>
</tbody>
</table>
Psychosocial interventions for fatigue during cancer treatment with palliative intent

**Barsevick 2004**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Design: RCT. Duration of study participation: duration of participation depended on type of cancer treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>USA, University of Utah health science center and Fox Chase Cancer Center. 396 individuals (aged 56.3 years, 85% female) beginning chemotherapy, radiotherapy, or concurrent therapy for breast, lung, colorectal, advanced prostate, gynaecologic, or testicular cancer or lymphoma.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Energy Conservation and Activity Management (ECAM): information provided to aid in the formation of an accurate representation of the symptom of fatigue, guide the formulation and implementation of a plan for energy conservation, and appraise the effectiveness of symptom-management efforts. Control group: information on nutrition and a healthy diet. No therapeutic nutritional information or information on symptom management.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>POMS Fatigue, Schwartz Cancer Fatigue Scale, General Fatigue Scale, and Functional Performance Inventory. Adverse events were not described.</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding: National Institute of Nursing Research (R01NR04573).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No information on the method of randomisation was provided.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No information on allocation concealment was provided.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>No information on blinding of outcome assessors was provided.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>More than 10% missing data for at least one data point on at least one fatigue measure, but used SAS mixed procedure restricted maximum likelihood method.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All data fully reported in the study.</td>
</tr>
<tr>
<td>Size of the study</td>
<td>Unclear risk</td>
<td>Between 50 and 199 participants randomised per treatment arm at baseline.</td>
</tr>
</tbody>
</table>
## Barsevick 2010

<table>
<thead>
<tr>
<th>Methods</th>
<th>Design: RCT. Duration of study participation: between 43-46 and 57-60 days depending on the length of the chemotherapy cycle.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>USA, Fox Chase Cancer Center. 292 patients (aged 53.9 years, 82% female) beginning a new chemotherapy regimen for breast, lung, colorectal, prostate, gynaecologic, bladder or testicular cancer, or lymphoma.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Energy and Sleep Enhancement (EASE): information about the symptom's identity, cause, and pattern to form a mental image of the symptom, identification and implementation of self-care strategies to manage the symptom. Evaluation of the effectiveness of the strategies and adjustment of either coping methods or symptom representation. Control intervention: information about nutrition and a healthy diet. Therapeutic nutritional information or information on symptom management not included.</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding: supported by the National Institute of Nursing Research (R01NR04573). Follow-up study of Barsevick 2004, building upon that intervention by introducing an additional intervention component (sleep modification strategies).</td>
</tr>
</tbody>
</table>

### Bias

<table>
<thead>
<tr>
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<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No information on the method of randomisation provided.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Random assignments generated by statistician and placed in sealed envelopes, numbered and selected sequentially for each stratification group. Unclear whether envelopes were opaque.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>No information on blinding of outcome assessors provided.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Less than 10% missing data and data were analysed using SAS mixed procedure (i.e., restricted maximum likelihood method).</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All data fully reported in the study.</td>
</tr>
<tr>
<td>Size of the study</td>
<td>Unclear risk</td>
<td>Between 50 and 199 participants randomised per treatment arm at baseline.</td>
</tr>
</tbody>
</table>
Psychosocial interventions for fatigue during cancer treatment with palliative intent

Bordeleau 2003

Methods
- Study design: RCT.
- Duration of study participation: 12 months.

Participants
- Canada, coordinated at Samuel Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto, and six other (regional) cancer centers.
- 237 women with metastatic breast cancer.

Interventions
- Supportive-Expressive Group Therapy (SEGT): weekly 90-minute therapist-led support group adhering to principles of supportive-expressive therapy. Intended to foster support among group members and encourage the expression of emotions about cancer and its effects on their lives. Relaxation exercise at the end of each seminar.
- Control group: no participation in a support group. Every six months, all women received educational materials about breast cancer and its treatment, relaxation, and nutrition. All study participants could receive any medical or psychosocial treatment deemed necessary.

Outcomes
- EORTC QLQ-C30 Fatigue, POMS Fatigue, EORTC-QLQ C30 Physical, Social, Role, Emotional, and Cognitive functioning.
- Adverse events were not described.

Notes
- Funding: Medical Research Council of Canada and the Canadian Breast Cancer Research Initiative.
- Summary data for the functional scales of the EORTC-QLQ-C30 were provided, but fatigue data of either the EORTC-QLQ-C30 or the POMS could not be provided (reason: “It would take too much time to retrieve the data”).
- Allegiance effect: This trial was designed to replicate the findings of a previous study on the effects of SEGT, thus therapists and/or researchers probably had some allegiance to SEGT.

Bias

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<tbody>
<tr>
<td>Random sequence generation</td>
<td>Unclear risk</td>
<td>No information on the method of randomisation provided.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Low risk</td>
<td>Randomisation performed centrally, stratified for study center and for the presence of visceral metastases.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Unclear risk</td>
<td>Questionnaires given to patients by the research assistant during baseline assessment, and mailed out four, eight, and 12 months after randomisation. No information on blinding of the research assistant provided.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>More than 10% missing data, but data analysed using SAS mixed model for repeated measures.</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Low risk</td>
<td>All data fully reported in the study.</td>
</tr>
<tr>
<td>Size of the study</td>
<td>Unclear risk</td>
<td>Between 50 and 199 participants randomised per treatment arm at baseline.</td>
</tr>
</tbody>
</table>
# Bruera 2013

**Methods**  
Study design: RCT.  
Duration of study participation: two weeks.

**Participants**  
USA, MD Anderson Cancer Center and Lundon B. Johnson General Hospital.  
190 patients with a diagnosis of advanced cancer and reporting fatigue.

**Interventions**  
Nursing Telephone Intervention (NTI): three components: (1) symptom assessment, (2) review of the types and dosages of medications and adverse events, (3) psychosocial support and patient education. Research nurse asked open-ended questions regarding general well being of the patient and family, listened empathetically, answered the patient’s questions, and provided supportive statements.  
Control group: nontherapeutic phone calls by a nonprofessional who assessed symptoms and asked about medications. No psychosocial support or education provided. If patients raised concerns, they were directed to discuss them with their physician.

**Outcomes**  
FACIT Fatigue and ESAS Fatigue. Adverse events were documented.

**Notes**  
Funding: National Institute of Health-National Institute of Nursing Research Grant (R01) and ACS Research Scholar Grant for Independent Investigators.  
Not eligible for meta-analysis. Summary data requested, but not could not be provided (reason: “No staff support to deal with the request”).

<table>
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<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Only reported that patients were randomly assigned to receive one of the four treatments but not how randomisation was performed.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not stated.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Reported that all of the members of the research team were blinded to treatment assignment (methylphenidate or placebo), but no information reported on blinding of outcome assessors for the nursing or control telephone intervention.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>More than 10% missing data, not described what was done with missing data, probably used complete-case analysis (only data from evaluable patients). Median differences between intervention and control group analysed using Wilcoxon two-sample tests.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All data fully reported in the study.</td>
</tr>
<tr>
<td>Size of the study</td>
<td>High risk</td>
<td>Fewer than 50 participants randomised per treatment arm at baseline.</td>
</tr>
</tbody>
</table>
Chan 2011

<table>
<thead>
<tr>
<th>Methods</th>
<th>Study design: RCT. Duration of study participation: three months.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Tuen Mun Hospital, Hong Kong. 140 patients with advanced lung cancer.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Psycho-educational intervention (PEI): PEI alters patients’ perceptions and sensations of symptoms through stress reduction; clarification of misconceptions; and the adoption of adaptive behaviours. A 40-minute educational package plus coaching of PMR delivered to patients within one week prior to the beginning of the course of radiotherapy, and reinforced three weeks after commencing radiotherapy. Usual care: mandatory individual briefing of the radiotherapy procedure and brief discussion of side effects by therapy radiographer.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Revised Piper Fatigue Scale Intensity subscale and SF-36 Physical functioning. Adverse events not described.</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding: Hong Kong Health Service Research Fund. Personal feedback intended in the intervention protocol, as confirmed by the original study investigator.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No explanation on the method of randomisation (lucky draw method) provided.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported how randomisation was performed.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Data collected by a research assistant blinded to group allocation.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Less than 10% missing data post-intervention. However, missing data imputed by a carry-forward method while missing data were not at random but related to outcomes that can lead to attrition bias.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All data fully reported in the study.</td>
</tr>
<tr>
<td>Size of the study</td>
<td>Unclear risk</td>
<td>Between 50 and 199 participants randomised per treatment arm at baseline.</td>
</tr>
</tbody>
</table>
Classen 2001

Methods

- Study design: RCT.
- Duration of study participation: 12 months.

Participants

- USA, Stanford University Medical Center.
- 125 women with metastatic breast cancer.

Interventions

- Supportive-Expressive Group Therapy (SEG): participants were encouraged to confront their problems, strengthen their relationships, and find enhanced meaning in their lives in a supportive environment. Neither coping strategies nor psycho-education was taught in a didactic manner. Self-hypnosis exercise at the end of each session.
- Control group: self-directed education intervention. Educational materials also offered to women in the treatment condition.

Outcomes

- POMS Fatigue. Adverse events not described.

Notes

- Allegiance effect: This trial was designed to replicate the findings of a previous study on the effects of SEG, thus therapists and/or researchers probably had some allegiance to SEG.

Bias

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Adaptive randomisation biased coin-design method.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Method of allocation concealment not stated.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>For the first two years of the study, baseline and post-baseline assessments completed on a computer. No information on blinding of the outcome assessors provided.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>More than 10% missing data. Slopes analysis used but only participants who provided at least one follow-up point included in the analysis.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All data fully reported in the study.</td>
</tr>
<tr>
<td>Size of the study</td>
<td>Unclear risk</td>
<td>Between 50 and 199 participants randomised per treatment arm at baseline.</td>
</tr>
</tbody>
</table>
Edelman 1999

<table>
<thead>
<tr>
<th>Method</th>
<th>Design: RCT. Duration of study participation: 12 months.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Australia, Royal North Shore Hospital. 124 women with metastatic breast cancer aged between 30 and 65 years.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Cognitive Behavioural Therapy (CBT): cognitive and behavioural techniques, expression of feelings, and building of group support. Manual, handouts, and homework provided. Emphasis on gaining a greater sense of control through problem solving and goal setting. Participants were instructed on effective communication strategies and encouraged to communicate assertively with friends, family members, and medical staff. Control group: No-therapy control group condition. Patients were informed about other community support groups that they could attend.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>POMS Fatigue. Adverse events not described.</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding: not specified.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>For every 20 patients a block randomisation procedure took place, with 10 being randomised to each treatment condition.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No information on allocation concealment provided.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>No information on blinding of outcome assessors provided.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>More than 10% missing data and data analysed using independent samples t-tests.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All data fully reported in the study.</td>
</tr>
<tr>
<td>Size of the study</td>
<td>Unclear risk</td>
<td>Between 50 and 199 participants randomised per treatment arm at baseline.</td>
</tr>
</tbody>
</table>
### Johansson 2008

<table>
<thead>
<tr>
<th>Methods</th>
<th>Design: RCT. Duration of study participation: 24 months.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Sweden, Uppsala University Hospital. 481 consecutive patients with newly diagnosed prostate, gastrointestinal or breast cancer. Women with a mammography finding requiring surgery could also be included.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Intervention group: Individual support included individual psychological support, intensified primary health care, and nutritional support for some patients, and implied extra contact with at least two or three different professionals, irrespective of the patients’ need for support. All patients were contacted by a project psychologist. Current problems identified jointly by the patients and the psychologist were the focus of the intervention. Techniques used were derived from cognitive behaviour therapy, including relaxation techniques, identification and challenging of negative automatic thoughts and activity scheduling and daily planning. Group rehabilitation conducted by a psychologist, physiotherapist and an oncology nurse. Sessions included cognitive behavioural techniques, light physical training and relaxation. In two of the sessions, a physician presented information about cancer and cancer treatment, and a dietician provided dietary advice. All sessions offered opportunities to disclose and discuss concerns with group leaders and members. Control group: standard care did not include regular follow-ups by a dietician or medical social worker. Patients could be referred to such services.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>EORTC QLQ-C30 Fatigue and EORTC QLQ-C30 Physical, Social, Role, Emotional and Cognitive functioning. Adverse events not described.</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding: Swedish Cancer Society. There were three different intervention groups: individual support, group rehabilitation, and combined individual support and group rehabilitation. We combined these three groups into one to have sufficient sample size for the subset of patients with incurable cancer receiving systemic treatment with palliative intent (combined intervention groups n=26 versus n=17 standard care group).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Patients randomised by an independent oncologic center (computer generated allocation schedule). Randomisation stratified for diagnosis and stage.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Patients randomised by an independent oncologic center (computer generated allocation schedule).</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Research nurse gave patients the baseline questionnaire with a prepaid envelope. At subsequent assessments, patients were contacted by one of the investigators by phone. Investigator gave instructions and mailed the questionnaires, written instructions and a prepaid envelope to the patients. No information on whether the investigators were blinded.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>More than 10% missing data and data analysed using one-way ANOVA with repeated measures.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All data fully reported in the study.</td>
</tr>
<tr>
<td>Size of the study</td>
<td>Unclear risk</td>
<td>Between 50 and 199 participants randomised per treatment arm at baseline.</td>
</tr>
</tbody>
</table>
Savard 2006

<table>
<thead>
<tr>
<th>Methods</th>
<th>Design: randomised clinical trial (May 1999 to June 2003). Duration of study participation: 36 weeks.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Canada, three cancer clinics: Hôpital St-Sacrement, L’Hôtel-Dieu de Québec and L’Hôtel-Dieu de Lévis. 45 patients with metastatic breast cancer reporting depressive symptoms.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Cognitive therapy: presentation of cognitive theory of emotions. Participants were encouraged to increase their level of daily activities and trained to identify their negative thoughts, to use cognitive restructuring, and to redefine their life goals. Future high-risk situations were identified, as well as strategies to cope with them. Control group: participants waited for a period corresponding to the duration of the intervention (8 weeks) and were reassessed on the study variables before receiving cognitive therapy.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Multidisciplinary Fatigue Inventory and EORTC QLQ-C30 Physical functioning. Adverse events not described.</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding: Canadian Breast Cancer Research Initiative (010436) and Canadian Institutes of Health Research.</td>
</tr>
</tbody>
</table>

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<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Prepared by principal investigator prior to study initiation using a computer-generated random numbers table.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Group allocation was contained in individually sealed envelopes. Unclear whether envelopes were sequentially sealed and opaque.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>At the post-treatment evaluation, the participants met the independent evaluator to complete self-report scales. Evaluator was blind to study objectives and procedures and the patients’ group allocation.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>More than 10% missing data. Linear mixed models used to analyse data, but only patients with at least one observation post-randomisation included in the analysis.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All data fully reported in the study.</td>
</tr>
<tr>
<td>Size of the study</td>
<td>High risk</td>
<td>Fewer than 50 participants randomised per treatment arm at baseline.</td>
</tr>
</tbody>
</table>
## Sharpe 2014

| Methods | Design: RCT.  
Duration of study participation: 48 weeks. |
|----------|-------------------------------------------------|
| Participants | Scotland, UK, three cancer centres.  
500 adults with a diagnosis of cancer, a good cancer prognosis (predicted survival of at least 12 months) and major depression of at least four weeks duration. |
| Interventions | Depression care: intensive, manualised, collaborative care–based multicomponent treatment programme specifically designed to be integrated with the patient’s cancer treatment. Nurses establish a therapeutic relationship with the patients, provide information about depression and its treatment, deliver brief evidence–based psychological interventions (problem-solving therapy and behavioural activation), and monitor patients’ progress. Psychiatrists supervise treatment, advise primary care physicians about prescribing antidepressants, and provide direct consultations to patients who are not improving. Usual care: participant’s primary care physician and oncologist were informed about the major depression diagnosis and asked to treat their patients as they normally would. Patient was encouraged to consult their primary care physician to obtain treatment. |
| Outcomes | EORTC QLQ–C30 Fatigue and EORTC QLQ–C30 Physical, Social, and Role functioning. Adverse events defined as deaths from any cause, admission to a psychiatric ward, or attempted suicide. |
| Notes | Funding: University of Edinburgh and NHS Lothian, Cancer Research UK (grant numbers CS547/A7375), Chief Scientist Office of the Scottish Government, and Scottish Mental Health Research Network funded by NHS Research Scotland. |

### Bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>
| Random sequence generation  
(selection bias) | Low risk | Database software algorithm allocated participants in a 1:1 ratio using a combination of stratification (by trial centre) and minimization (by age, primary cancer, and sex). |
| Allocation concealment  
(selection bias) | Low risk | Secure web-based randomisation database implemented by a trials unit. |
| Blinding of outcome assessment  
(detection bias) | Low risk | Trial statistician and staff who collected outcome data masked to allocated interventions; however, participants could not be masked because of the nature of depression care for people with cancer. |
| Incomplete outcome data  
(attrition bias) | Low risk | Less than 10% missing data. Analysis of covariance used for data analysis. In addition, sensitivity analysis using multiple imputation performed. |
| Selective reporting  
(reporting bias) | Low risk | All data fully reported in the study. |
| Size of the study | Low risk | More than 200 participants randomised per treatment arm at baseline. |
Spiegel 1981

<table>
<thead>
<tr>
<th>Methods</th>
<th>Design: RCT. Duration of study participation: 12 months.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>USA, Stanford University School of Medicine. 86 women with metastatic breast cancer.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Psychosocial Support Group (PSG): designed to be supportive, with a high degree of cohesion and relatively little confrontation and here-and-now interpersonal exploration. Interaction in the group often contained a considerable amount of self-disclosure and sharing of mutual fears and concerns. Control group: Not described.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>POMS Fatigue. Adverse events not described.</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding: National Cancer Institute (N01-CN-55313 [DHEW]) and Veterans Administration.</td>
</tr>
</tbody>
</table>

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<tr>
<th>Bias</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No information on the method of randomisation provided.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No information on allocation concealment provided.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>No information on blinding of outcome assessors provided.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>More than 10% missing data. Slopes analysis used to analyse data, but only participants who completed at least two assessments included in the analysis.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All data fully reported in the study.</td>
</tr>
<tr>
<td>Size of the study</td>
<td>High risk</td>
<td>Fewer than 50 participants randomised per treatment arm at baseline.</td>
</tr>
</tbody>
</table>
Steel 2016

Methods
Design: RCT.
Duration of study participation: six months.

Participants
USA, University of Pittsburgh Medical Center's Liver Cancer Center.
261 patients (aged 61 years, 73% male) with hepatocellular carcinoma, cholangiocarcinoma, gallbladder carcinoma, neuroendocrine carcinoma, pancreatic carcinoma, or other primary cancers that had metastasized to the liver (e.g. ovarian, breast, and colorectal cancer).

Interventions
Web-based stepped collaborative care intervention: access to a psycho-educational web site and to a collaborative care coordinator with training and experiences with cognitive behavioural therapy and psycho-oncology.
Control group: usual care provided by the medical team. For ethical reasons, patients scoring high on a depression or pain measure were contacted by a care coordinator who provided education about the symptoms and referral options.

Outcomes
FACT Fatigue. Adverse events not described.

Notes
Funding: National Cancer Institute (K07CA118576, R21CA127046, and P30CA047904).

Bias

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<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>The patients randomly assigned via a block randomisation design according to sex and vascular invasion.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Allocation concealment achieved through the use of a random number table that assigned consecutive patients across the group. A research assistant who was not part of the study placed the trial assignments in opaque envelopes consecutively per group.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>All data collected by trained interviewers using a structured computerized interview. The interviewers were blinded to study arm assignment.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>More than 10% missing data. Two separate general linear mixed models analyses performed: first with all participants and then with patients with clinically significant symptoms at baseline.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Effects of the intervention only reported for the subgroup of patients with clinically relevant symptoms at baseline (n=132), results for the entire sample not presented but were provided upon request.</td>
</tr>
<tr>
<td>Size of the study</td>
<td>Unclear risk</td>
<td>Between 50 and 199 participants randomised per treatment arm at baseline.</td>
</tr>
</tbody>
</table>
Psychosocial interventions for fatigue during cancer treatment with palliative intent

Walker 2014

Methods
Design: RCT.
Duration of study participation: 32 weeks.

Participants
Scotland, UK, three cancer centres.
142 adults with primary lung cancer, a predicted survival of at least three months and major depression for four weeks or longer.

Interventions
Depression care: multicomponent, systematic, team-delivered treatment programme based on the collaborative care model and integrated with lung cancer care. Nurses establish a therapeutic relationship with the participants, provide information about depression and its treatment, deliver brief evidence-based psychological interventions (problem-solving therapy and behavioural activation), and monitor patients’ progress. Psychiatrists supervise treatment, advise primary care physicians about prescribing to ensure rapid initiation and proactive adjustment of antidepressants, and provide direct consultations to patients who are not progressing.
Usual care: participant’s primary care physician and oncologist were informed of the diagnosis of major depression and asked to treat them as they normally would. Patient was encouraged to see their primary care physician to obtain treatment.

Outcomes
EORTC QLQ-C30 Fatigue and EORTC QLQ-C30 Physical, Social, and Role functioning. Adverse events defined as death from any cause, admission to a psychiatric ward, or attempted suicide.

Notes
Funding: University of Edinburgh, NHS Lothian, Cancer Research UK (grant numbers C5547/A7375 and C25786/A10093), Chief Scientist Office of the Scottish Government, and Scottish Mental Health Research Network funded by NHS Research Scotland.

Bias

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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Database software algorithm allocated participants in a 1:1 ratio using a combination of stratification (by trial centre) and minimization (by age, sex, and lung cancer type).</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Secure web-based randomisation database implemented by a trials unit.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Trial statistician and staff who collected outcome data masked to allocated interventions; however, participants could not be masked because of the nature of depression care for people with cancer.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>More than 10% missing data. A summary measure approach used in the analysis of covariance, which copes with missing data and sensitivity analyses using multiple imputation were performed.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All data fully reported in the study.</td>
</tr>
<tr>
<td>Size of the study</td>
<td>Unclear risk</td>
<td>Between 50 and 199 participants randomised per treatment arm at baseline.</td>
</tr>
</tbody>
</table>
# CHARACTERISTICS OF EXCLUDED STUDIES

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adamsen 2009</td>
<td>Mixed-sample study. None of the incurable cancer patients were receiving active cancer treatment.</td>
</tr>
<tr>
<td>Anderson 2015</td>
<td>Unable to determine whether intervention fulfilled our formulated criteria, no response received from study investigators.</td>
</tr>
<tr>
<td>Berglund 2007</td>
<td>Mixed-sample study. Study investigators were unable to retrieve the data.</td>
</tr>
<tr>
<td>Bigatao 2016</td>
<td>Unable to determine whether intervention fulfilled our formulated criteria and whether the study sample also included patients with incurable cancer.</td>
</tr>
<tr>
<td>Brown 2006</td>
<td>Does not meet our formulated criteria for psychosocial intervention. Study investigators confirmed that personal feedback was not intended.</td>
</tr>
<tr>
<td>Cunningham 1989</td>
<td>Unknown whether study sample also includes patients with incurable cancer. Unable to retrieve professional contact address of the original study investigators.</td>
</tr>
<tr>
<td>De Moor 2001</td>
<td>Did not meet our formulated criteria for psychosocial intervention.</td>
</tr>
<tr>
<td>De Raaf 2013</td>
<td>Did not meet our formulated criteria for psychosocial intervention. Study investigators confirmed that personal feedback was not intended.</td>
</tr>
<tr>
<td>Decker 1992</td>
<td>Mixed-sample study. Unable to retrieve professional contact address of the study investigators.</td>
</tr>
<tr>
<td>Fernandez 2011</td>
<td>No RCT, study investigators confirmed that all baseline measures were taken after randomization.</td>
</tr>
<tr>
<td>Focan 2015</td>
<td>Unable to determine whether intervention fulfilled our eligibility criteria, no detailed intervention content information was received from study investigators.</td>
</tr>
<tr>
<td>Forester 1985</td>
<td>Unknown whether study sample also included patients with incurable cancer. Unable to retrieve professional contact address of the study investigators.</td>
</tr>
<tr>
<td>Gaston-Johansson 2000</td>
<td>Mixed-sample study, no response received from study investigators.</td>
</tr>
<tr>
<td>Given 2002</td>
<td>Mixed-sample study, study investigators not willing to provide data. Entire study sample included &lt; 80% of patients with incurable cancer, thus excluded from the review.</td>
</tr>
<tr>
<td>Godino 2006</td>
<td>Unknown whether study sample also included patients with incurable cancer, no response received from study investigators.</td>
</tr>
<tr>
<td>Oh 2010</td>
<td>Unknown whether study sample also included patients with incurable cancer, no response received from study investigators.</td>
</tr>
<tr>
<td>Ream 2006</td>
<td>Mixed-sample study, request for separate summary data sent to the study investigators but no response received.</td>
</tr>
<tr>
<td>Ream 2015</td>
<td>Unknown whether study sample also included patients with incurable cancer, no response received from study investigators.</td>
</tr>
<tr>
<td>Serfaty 2012</td>
<td>Unknown whether study sample also included patients with incurable cancer. Study investigators confirmed not knowing whether incurable cancer patients were part of the sample.</td>
</tr>
<tr>
<td>Strong 2008</td>
<td>Mixed-sample study, study investigators unable to provide data.</td>
</tr>
<tr>
<td>Yorke 2015</td>
<td>Did not meet formulated criteria for receiving cancer treatment. Study investigators confirmed that none of the participants were receiving cancer treatment with palliative intent during the intervention.</td>
</tr>
</tbody>
</table>
CHARACTERISTICS OF ONGOING STUDIES

Poort

**Study name**: TIRED study

**Methods**: RCT

**Participants**: Netherlands, Radboud university medical center with sites set up across the Netherlands. 219 patients with a diagnosis of incurable cancer and reporting severe fatigue.

**Interventions**: Cognitive behavioural therapy (CBT): 12-week CBT intervention designed to treat severe fatigue during systemic cancer treatment with palliative intent for incurable cancer. CBT consists of 10 individual, clinic-delivered sessions and will be delivered by trained psychologists. Control condition: usual care. Participants may be referred to psychological or exercise interventions by their general practitioner or oncologist.

**Outcomes**: Checklist Individual Strength, EORTC QLQ-C30 Fatigue, Sickness Impact Profile, and EORTC QLQ-C30 Physical, Social, Role, Emotional, and Cognitive functioning.

**Starting date**: January 2013, recruitment ongoing.

**Contact information**: Hanneke Poort, MSc, Department of Medical Psychology, Radboud university medical center, Nijmegen, The Netherlands.

**Notes**: Funding: Dutch Cancer Society (KUN2011-5259). This study is performed by five of the review authors (HP, MP, GB, SV, HK).

Serfaty

**Study name**: CanTalk study

**Methods**: RCT

**Participants**: UK, University College London with sites set up across England. 230 patients with advanced, non-curative cancer and a clinical diagnosis of depression.

**Interventions**: Cognitive behavioural therapy (CBT) in addition to treatment as usual (TAU): up to 12 sessions of individual CBT delivered face to face or on the telephone over three months. TAU: all patients receive TAU from oncology teams and from their general practitioners (GPs). Specific psychological support may be available for those who present with psychological needs at any time.

**Outcomes**: Beck Depression Inventory-II single-item for fatigue.

**Starting date**: July 2012, recruitment completed.

**Contact information**: Dr Marc Serfaty, Division of Psychiatry, University College London, London, UK.

**Notes**: Funding: National Institute for Health Research (NIHR) Health Technology Assessment Programme.
### SUMMARY OF FINDINGS TABLE

**Psychosocial interventions compared with control intervention for fatigue during cancer treatment with palliative intent**

**Patient or population**: patients with incurable cancer receiving cancer treatment with palliative intent  
**Settings**: university-affiliated hospitals, cancer centres, public hospitals  
**Intervention**: psychosocial interventions  
**Comparison**: usual care or control conditions (not being a psychosocial intervention)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Not known</td>
<td>Not known</td>
<td>Fatigue in the psychosocial interventions group was lower than in the control group (SMD -0.25, 95% CI -0.50 to 0.00)</td>
<td>535 (12)</td>
<td>⊘⊝⊝⊝ very low&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>Not known</td>
<td>Not known</td>
<td>Physical functioning in the psychosocial interventions group was higher (SMD 0.32, 95% CI 0.01 to 0.63)</td>
<td>307 (7)</td>
<td>⊘⊝⊝⊝ very low&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Social functioning</td>
<td>Not known</td>
<td>Not known</td>
<td>Social functioning in the psychosocial interventions group was higher (MD 4.16, 95% CI -11.20 to 19.53)</td>
<td>141 (4)</td>
<td>⊘⊝⊝⊝ very low&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Role functioning</td>
<td>Not known</td>
<td>Not known</td>
<td>Role functioning in the psychosocial interventions group was higher (MD 3.49, 95% CI -12.78 to 19.76)</td>
<td>143 (4)</td>
<td>⊘⊝⊝⊝ very low&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>Not known</td>
<td>Not known</td>
<td>Emotional functioning in the psychosocial interventions group was lower (SMD -0.11, 95% CI -0.56 to 0.35)</td>
<td>115 (3)</td>
<td>⊘⊝⊝⊝ very low&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>Not known</td>
<td>Not known</td>
<td>Cognitive functioning in the psychosocial interventions group was lower (MD -2.23, 95% CI -12.52 to 8.06)</td>
<td>86 (2)</td>
<td>⊘⊝⊝⊝ very low&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Adverse events**:  
See comment  
Not estimable  
No data available for meta-analysis.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). CI: confidence interval; SMD: standardized mean difference; MD: mean difference.

<sup>1</sup> Downgraded once: Unclear risk of selection bias.  
<sup>2</sup> Downgraded twice: Imprecision due to very sparse data.
DATA AND ANALYSES

1 Fatigue

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Post-intervention</td>
<td>12</td>
<td>535</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.25 [-0.50, 0.00]</td>
</tr>
<tr>
<td>1.2 First follow-up</td>
<td>4</td>
<td>147</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.66 [-1.00, -0.32]</td>
</tr>
<tr>
<td>1.3 Second follow-up</td>
<td>2</td>
<td>91</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.41 [-1.12, 0.30]</td>
</tr>
</tbody>
</table>

2 Physical functioning

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Post-intervention</td>
<td>7</td>
<td>307</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>0.32 [0.01, 0.63]</td>
</tr>
<tr>
<td>2.2 First follow-up</td>
<td>2</td>
<td>122</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>0.37 [-0.20, 0.94]</td>
</tr>
</tbody>
</table>

3 Social functioning

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Post-intervention</td>
<td>4</td>
<td>141</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>4.16 [-11.20, 19.53]</td>
</tr>
</tbody>
</table>

4 Role functioning

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1 Post-intervention</td>
<td>4</td>
<td>143</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>3.49 [-12.78, 19.76]</td>
</tr>
</tbody>
</table>

5 Emotional functioning

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1 Post-intervention</td>
<td>3</td>
<td>115</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.11 [-0.56, 0.35]</td>
</tr>
</tbody>
</table>

6 Cognitive functioning

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1 Post-intervention</td>
<td>2</td>
<td>86</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-2.23 [-12.52, 8.06]</td>
</tr>
</tbody>
</table>
### 7 Subgroup analyses

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1 Fatigue post-intervention</td>
<td>12</td>
<td>535</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.25 [-0.50, 0.00]</td>
</tr>
<tr>
<td>7.1.1 short intervention duration</td>
<td>3</td>
<td>163</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.12 [-0.72, 0.48]</td>
</tr>
<tr>
<td>7.1.2 intermediate-long intervention duration</td>
<td>9</td>
<td>372</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.28 [-0.57, 0.02]</td>
</tr>
<tr>
<td>7.2 Fatigue post-intervention</td>
<td>11</td>
<td>507</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.27 [-0.53, -0.00]</td>
</tr>
<tr>
<td>7.2.1 group intervention delivery</td>
<td>3</td>
<td>195</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.33 [-0.78, 0.11]</td>
</tr>
<tr>
<td>7.2.2 individual intervention delivery</td>
<td>8</td>
<td>312</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.22 [-0.58, 0.14]</td>
</tr>
<tr>
<td>7.3 Fatigue post-intervention</td>
<td>12</td>
<td>535</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.25 [-0.50, 0.00]</td>
</tr>
<tr>
<td>7.3.1 monodisciplinary intervention type</td>
<td>9</td>
<td>452</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.20 [-0.44, 0.04]</td>
</tr>
<tr>
<td>7.3.2 multidisciplinary intervention type</td>
<td>3</td>
<td>83</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.41 [-1.30, 0.47]</td>
</tr>
<tr>
<td>7.4 Fatigue post-intervention</td>
<td>12</td>
<td>535</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.25 [-0.50, 0.00]</td>
</tr>
<tr>
<td>7.4.1 fatigue specific intervention aim</td>
<td>5</td>
<td>232</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.09 [-0.48, 0.31]</td>
</tr>
<tr>
<td>7.4.2 other intervention aim</td>
<td>7</td>
<td>303</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.37 [-0.72, -0.02]</td>
</tr>
<tr>
<td>7.5 Fatigue first follow-up</td>
<td>7</td>
<td>270</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.53 [-0.78, -0.28]</td>
</tr>
<tr>
<td>7.5.1 no additional sessions</td>
<td>4</td>
<td>147</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.66 [-1.00, -0.32]</td>
</tr>
<tr>
<td>7.5.2 additional sessions</td>
<td>3</td>
<td>123</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.43 [-0.90, 0.04]</td>
</tr>
<tr>
<td>7.6 Fatigue second follow-up</td>
<td>5</td>
<td>202</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.26 [-0.58, 0.07]</td>
</tr>
<tr>
<td>7.6.1 no additional sessions</td>
<td>2</td>
<td>91</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.41 [-1.12, 0.30]</td>
</tr>
<tr>
<td>7.6.2 additional sessions</td>
<td>3</td>
<td>111</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.22 [-0.74, 0.30]</td>
</tr>
</tbody>
</table>

### 8 Sensitivity analyses

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1 Fatigue post-intervention</td>
<td>9</td>
<td>476</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.30 [-0.59, 0.00]</td>
</tr>
<tr>
<td>8.2 Fatigue first follow-up</td>
<td>1</td>
<td>103</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.70 [-1.10, -0.30]</td>
</tr>
<tr>
<td>8.3 Fatigue second follow-up</td>
<td>1</td>
<td>81</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.23 [-0.67, 0.22]</td>
</tr>
</tbody>
</table>
APPENDICES

1 GRADE system

The GRADE system uses the following criteria for assigning grades of evidence:

- High: we are very confident that the true effect lies close to that of the estimate of the effect;
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

The grade of evidence is decreased further if the following are present:

- Serious (-1) or very serious (-2) limitation to study quality;
- Important inconsistency (-1);
- Some (-1) or major (-2) uncertainty about directness;
- Imprecise or sparse data (-1);
- High probability of reporting bias (-1).

The grade of evidence may be increased if:

- Strong evidence of association: significant relative risk of >2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1);
- Very strong evidence of association: significant relative risk of >5 (< 0.2) based on direct evidence with no major threats to validity (+2);
- Evidence of a dose response gradient (+1);
- All plausible confounders would have reduced the effect (+1).
2 CENTRAL search strategy

#1 ((neoplas* or cancer*)):TI,AB,KY
#2 (carcinoma* or tumour* or adenocarcinoma*):TI,AB,KY
#3 (leukemi* or leukaemia* or lymphoma*):TI,AB,KY
#4 (tumor* or malignan* or melanoma* or sarcoma*):TI,AB,KY
#5 ("bone marrow transplant*" or "stem cell transplant*"):TI,AB,KY
#6 MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES
#7 MESH DESCRIPTOR Bone Marrow Transplantation
#8 MESH DESCRIPTOR Stem Cell Transplantation EXPLODE ALL TREES
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10 MESH DESCRIPTOR Fatigue EXPLODE ALL TREES
#11 ((fatigue* or asthenia or asthenic or astheni*)):TI,AB,KY
#12 ((exhaustion or exhausted)):TI,AB,KY
#13 (((loss adj4 energy) or (loss adj4 vitality)):TI,AB,KY
#14 ((weary or weariness or weakness)):TI,AB,KY
#15 ((apathy or apathetic or lassitude or lethargic or lethargy)):TI,AB,KY
#16 ((sleepy or sleepiness or drowsy or drowsiness)):TI,AB,KY
#17 ((tired or tiredness)):TI,AB,KY
#18 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19 MESH DESCRIPTOR Psychotherapy EXPLODE ALL TREES
#20 ((psychosocial* or psycho-social*)):TI,AB,KY
#21 management* or psychotherapy* or “self
#22 educati* or psychoeducat* or relaxation
#23 counsel$ or (behaviour$ adj4 therap$) or “autogenic training”
#24 (behavior* adj4 therap*) or (relax* adj4 therap*) or (relax* adj4 treatment*) or (support* adj4 group*)
#25 management” or psychotherapy* or “self
#26 imagery or “energy conservation” or “stress management” or psychotherapy* or “self care” or “self help”
#27 “nursing support”
#28 biofeedback or educati* or psychoeducat* or relaxation therap*
#29 “nursing intervention” or “nursing support”
#30 #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
#31 #9 AND #18 AND #30
3 MEDLINE search strategy

1 exp Neoplasms/
2 Bone Marrow Transplantation/
3 exp Stem Cell Transplantation/
4 (neoplas$ or cancer$ or carcinoma$ or tumour$ or adenocarcinoma$ or leukemi$ or leukaemia$ or lymphoma$ or tumor$ or malignant$ or melanoma$ or sarcoma$ or “bone marrow transplant$” or “stem cell transplant$”).mp.
5 or/1-4
6 exp Fatigue/
7 (fatigue$ or asthenia or asthenic or astheni$).mp.
8 (exhaustion or exhausted).mp.
9 ((loss adj4 energy) or (loss adj4 vitality)).mp.
10 (weary or weariness or weakness).mp.
11 (apathy or apathetic or lassitude or lethargic or lethargy).mp.
12 (sleepy or sleepiness or drowsy or drowsiness).mp.
13 (tired or tiredness).mp.
14 or/6-13
15 exp Psychotherapy/
16 (psychosocial$ or psycho-social$).mp.
17 (counsel$ or (behaviour$ adj4 therap$) or “autogenic training” or (behavior$ adj4 therap$) or (relax$ adj4 therap$) or (relax$ adj4 treatment$) or (support$ adj4 group$) or imagery or “energy conservation” or “stress management” or psychotherapy$ or “self care” or “self help” or biofeedback or educati$ or psychoeducat$ or relaxation therap$ or “nursing intervention” or “nursing support$”).mp.
18 or/15-17
19 5 and 14 and 18
20 randomized controlled trial.pt.
21 controlled clinical trial.pt.
22 randomized.ab.
23 placebo.ab.
24 drug therapy.fs.
25 randomly.ab.
26 trial.ab.
27 groups.ab.
28 20 or 21 or 22 or 24 or 25 or 26 or 27
29 exp animals/ not humans.sh.
30 28 not 29
31 19 and 30
4 EMBASE search strategy
1 exp Neoplasms/
2 Bone Marrow Transplantation/
3 exp Stem Cell Transplantation/
4 (neoplas$ or cancer$ or carcinoma$ or tumour$ or adenocarcinoma$ or leukemi$ or leukaemia$ or lymphoma$ or tumor$ or malignant$ or melanoma$ or sarcoma$ or “bone marrow transplant$” or “stem cell transplant$”).mp.
5 or/1-4
6 exp Fatigue/
7 (fatigue$ or asthenia or asthenic or astheni$).mp.
8 (exhaustion or exhausted).mp.
9 ((loss adj4 energy) or (loss adj4 vitality)).mp.
10 (weary or weariness or weakness).mp.
11 (apathy or apathetic or lassitude or lethargic or lethargy).mp.
12 (sleepy or sleepiness or drowsy or drowsiness).mp.
13 (tired or tiredness).mp.
14 or/6-13
15 exp Psychotherapy/
16 (psychosocial$ or psycho-social$).mp.
17 (counsel$ or (behaviour$ adj4 therap$) or “autogenic training” or (behavior$ adj4 therap$) or (relax$ adj4 therap$) or (relax$ adj4 treatment$) or (support$ adj4 group$) or imagery or “energy conservation” or “stress management” or psychotherapy$ or “self care” or “self help” or biofeedback or educati$ or psychoeducat$ or relaxation therap$ or “nursing intervention” or “nursing support”).mp.
18 or/15-17
19 5 and 14 and 18
20 random$.tw.
21 factorial$.tw.
22 crossover$.tw.
23 cross over$.tw.
24 cross-over$.tw.
25 placebo$.tw.
26 (doubl$ adj blind$).tw.
27 (singl$ adj blind$).tw.
28 assign$.tw.
29 allocat$.tw.
30 volunteer$.tw. (201718)
31 Crossover Procedure/ (45499)
32 double-blind procedure.tw. (229)
33 Randomized Controlled Trial/ (391636)
34 Single Blind Procedure/ (21265)
35 or/20-34 (1643586)
36 (animal/ or nonhuman/) not human/ (4924135)
37 35 not 36 (1458151)
38 19 and 37 (956)

5 CINAHL search strategy
S28 S18 AND S27
S27 S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26
S26 (allocat* random*)
S25 (MH “Quantitative Studies”)
S24 (MH “Placebos”)
S23 placebo*
S22 (random* allocat*)
S21 (MH “Random Assignment”)
S20 (Randomi?ed control* trial*)
S19 (singl* blind* ) or (doubl* blind* ) or (tripl* blind* ) or (trebl* blind* ) or (trebl* mask* ) or (tripl*
mask* ) or (doubl* mask* ) or (singl* mask* )
S18 S5 AND S13 AND S17
S17 S14 OR S15 OR S16
S16 (counse1$ or (behaviour$ adj4 therap$) or “autogenic training” or (behavior* N4 therap*) or (relax* N4 therap*) or (relax* N4 treatment*) or (support* N4 group*) or imagery or “energy conservation” or “stress management” or psychotherapy* or “self care” or “self help” or biofeedback or educati* or psychoeducat* or relaxation therap* or “nursing intervention” or “nursing support”)
S15 psychosocial* or psycho-social*
S14 (MH “Psychotherapy+”)
S13 S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12
S12 tired or tiredness
S11 sleepy or sleepiness or drowsy or drowsiness
S10 apathy or apathetic or lassitude or lethargic or lethargy
S9 weary or weariness or weakness
S8 (loss N4 energy) or (loss N4 vitality)
S7 exhaustion or exhausted
S6 (fatigue* or asthenia or asthenic or astheni*)
S5 S1 OR S2 OR S3 OR S4
S4 (neoplas* or cancer* or carcinoma* or tumour* or adenocarcinoma* or leukemi* or leukaemia* or lymphoma* or tumor* or malignan* or melanoma* or sarcoma* or “bone marrow transplant”* or “stem cell transplant”*)
S3 (MH “Hematopoietic Stem Cell Transplantation”)
S2 (MH “Bone Marrow Transplantation”)
S1 (MH “Neoplasms”)

Psychosocial interventions for fatigue during cancer treatment with palliative intent
6 PsycINFO search strategy

1 exp Neoplasms/
2 (neoplas$ or cancer$ or carcinoma$ or tumour$ or adenocarcinoma$ or leukemi$ or leukaemia$ or lymphoma$ or tumor$ or malignan$ or melanoma$ or sarcoma$ or “bone marrow transplant$” or “stem cell transplant$”).mp.
3 exp Fatigue/
4 (fatigue$ or asthenia or asthenic or astheni$).mp.
5 (exhaustion or exhausted).mp.
6 ((loss adj4 energy) or (loss adj4 vitality)).mp.
7 (weary or weariness or weakness).mp.
8 (apathy or apathetic or lassitude or lethargic or lethargy).mp.
9 (sleepy or sleepiness or drowsy or drowsiness).mp.
10 (tired or tiredness).mp.
11 or/3-10
12 exp Psychotherapy/
13 (psychosocial$ or psycho-social$).mp.
14 (counsel$ or (behaviour$ adj4 therap$) or “autogenic training” or (behavior$ adj4 therap$) or (relax$ adj4 therap$) or (relax$ adj4 treatment$) or (support$ adj4 group$) or imagery or “energy conservation” or “stress management” or psychotherapy$ or “self care” or “self help” or biofeedback or educati$ or psychoeducat$ or relaxation therap$ or “nursing intervention” or “nursing support$”).mp.
15 or/12-14
16 1 or 2
17 11 and 15 and 16
18 clinical trials/
19 (randomis* or randomiz*).tw.
20 (random$ adj3 (allocat$ or assign$)).tw.
21 ((clinic$ or control$) adj trial$).tw.
22 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
23 (crossover$ or “cross over$”).tw.
24 random sampling/
25 Experiment Controls/
26 Placebo/
27 placebo$.tw.
28 exp program evaluation/
29 treatment effectiveness evaluation/
30 ((effectiveness or evaluat$) adj3 (stud$ or research$)).tw.
31 or/18-30
32 17 and 31
REFERENCES

**Included studies**

**Armes 2007**


**Barsevick 2004**


**Barsevick 2010**


**Bordeleau 2003**


**Bruera 2013**


**Chan 2011**


**Classen 2001**


**Edelman 1999**


**Johannsson 2008**


Chapter 6

**Savard 2006**

**Sharpe 2014**

**Spiegel 1981**

**Steel 2016**

**Walker 2014**

**Excluded studies**

**Adamsen 2009**

**Anderson 2015**

**Berglund 2007**

**Bigatao 2016**

**Brown 2006**
Psychosocial interventions for fatigue during cancer treatment with palliative intent

Cunningham 1989

Decker 1992

De Moor 2001

De Raaf 2013

Fernandez 2011

Focan 2015

Forester 1985

Gaston-Johansson 2000

Given 2002

Godino 2006

Oh 2010

Ream 2006
Ream 2015

Serfaty 2012

Strong 2008

Yorke 2015

Ongoing studies
Poort

Serfaty

Additional references
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Psychosocial interventions for fatigue during cancer treatment with palliative intent

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Psychosocial interventions for fatigue during cancer treatment with palliative intent
CHAPTER 7

STUDY PROTOCOL OF THE TIRED STUDY:
A RANDOMISED CONTROLLED TRIAL COMPARING
EITHER GRADED EXERCISE THERAPY FOR
SEVERE FATIGUE OR COGNITIVE BEHAVIOUR
THERAPY WITH USUAL CARE IN PATIENTS
WITH INCURABLE CANCER

Hanneke Poort, Stans Verhagen, Marlies Peters,
Martine Goedendorp, Rogier Donders, Maria Hopman,
Ria Nijhuis-van der Sanden, Thea Berends, Gijs Bleijenberg,
Hans Knoop

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ABSTRACT

Background
Fatigue is a common and debilitating symptom for patients with incurable cancer receiving systemic treatment with palliative intent. There is evidence that non-pharmacological interventions such as graded exercise therapy (GET) or cognitive behaviour therapy (CBT) reduce cancer-related fatigue in disease-free cancer patients and in patients receiving treatment with curative intent. These interventions may also result in a reduction of fatigue in patients receiving treatment with palliative intent, by improving physical fitness (GET) or changing fatigue-related cognitions and behaviour (CBT). The primary aim of our study is to assess the efficacy of GET or CBT compared to usual care (UC) in reducing fatigue in patients with incurable cancer.

Methods
The TIRED study is a multicentre three-armed randomised controlled trial (RCT) for incurable cancer patients receiving systemic treatment with palliative intent. Participants will be randomised to GET, CBT, or UC. In addition to UC, the GET group will participate in a 12-week supervised exercise programme. The CBT group will receive a 12-week CBT intervention in addition to UC. Primary and secondary outcome measures will be assessed at baseline, post-intervention (14 weeks), and at follow-up assessments (18 and 26 weeks post-randomisation). The primary outcome measure is fatigue severity (Checklist Individual Strength subscale fatigue severity). Secondary outcome measures are fatigue (EORTC-QLQ-C30 subscale fatigue), functional impairments (Sickness Impact Profile total score, EORTC-QLQ-C30 subscale emotional functioning, subscale physical functioning) and quality of life (EORTC-QLQ-C30 subscale QoL). Outcomes at 14 weeks (primary endpoint) of either treatment arm will be compared to those of UC participants. In addition, outcomes at 18 and 26 weeks (follow-up assessments) of either treatment arm will be compared to those of UC participants.

Discussion
To our knowledge, the TIRED study is the first RCT investigating the efficacy of GET and CBT on reducing fatigue during treatment with palliative intent in incurable cancer patients. The results of this study will provide information about the possibility and efficacy of GET and CBT for severely fatigued incurable cancer patients.
BACKGROUND

Cancer is a leading cause of mortality worldwide, with 8.2 million deaths in 2013 [1]. As a result of improvements in treatment options for certain cancers, substantial progress has been made in curative treatment of cancer. Despite these positive developments, a substantial subgroup of cancer patients will (eventually) be diagnosed with incurable cancer. The medical treatment of incurable cancer has a palliative intention, with prolonging life as one of its main aims [2]. For some cancer types, advances in cancer treatment with palliative intent have resulted in an extended period of life, resulting in more long-term or chronic cancer treatment. Next to prolonging life, treatment of incurable cancer should also be aimed at maintaining quality of life for as long as possible and relieving physical and psychological symptoms [2]. As a result of the longer-term treatment of incurable cancer patients, aspects regarding quality of life and symptom management become even more important.

Fatigue in patients with incurable cancer

Fatigue is one of the most commonly reported symptoms during systemic treatment for incurable cancer, being reported by up to 99% of patients [3-7]. There are various ways to define fatigue, but cancer-related fatigue (CRF) is a term that is most widely used to address this symptom. The National Comprehensive Cancer Network (NCCN) defines CRF as “a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” [8]. Studies show that CRF is among the most distressing symptoms [3, 9, 10] and is associated with reduced quality of life, poor performance status, and difficulty performing daily activities [3, 4, 11]. Many factors are likely to contribute to CRF in patients with incurable cancer. The multiple causes of CRF can result from the underlying disease, from secondary factors such as anaemia, infection, dehydration, and treatment side effects, or from loss of muscle mass. Apart from these physical factors, depression and anxiety can also contribute to CRF. There is also evidence suggesting that cognitive and behavioural factors, such as sleeping problems, fatigue catastrophising, and inappropriate coping are related to fatigue in patients with incurable cancer [12].

Management of CRF in incurable cancer patients should first focus on identifying and treating somatic causes, for example anaemia or hypothyroidism [8]. Yet, often no somatic cause for CRF can be found. When no somatic cause can be identified, the management of CRF can involve pharmacological treatment or non-pharmacological interventions. Thus far, no recommendation for a specific drug treatment for fatigue in palliative care patients could be given [13]. There is also no evidence-based non-pharmacological intervention for CRF in incurable cancer patients. Two non-pharmacological approaches, Graded Exercise Therapy (GET) and Cognitive
Chapter 7

Behaviour Therapy (CBT), seem promising interventions based on findings from studies addressing CRF in other cancer patients that will be discussed below.

Exercise interventions for CRF in cancer patients

In contrast to the old advice to ‘get plenty of rest’ during cancer treatment, patients are now encouraged to optimise levels of physical activity [8]. A low level of physical activity during cancer treatment can lead to decreased physical functioning by a substantial loss of cardiopulmonary fitness and muscle mass [14]. On the other hand, increasing physical activity has been suggested as helpful in reducing CRF by improving physical capacity, resulting in a reduced effort to perform everyday activities [8]. Cramp & Byron-Daniel (2012) suggested that exercise interventions can help to reduce CRF both during and after adjuvant treatment for cancer [15]. Efficacy of exercise interventions for the subgroup of patients receiving cancer treatment with palliative intent was not examined in this Cochrane systematic review. Nonetheless, a systematic review by Lowe et al. (2009) did provide evidence that exercise interventions are feasible in patients with incurable cancer as the majority of participants were able to tolerate various physical activity interventions [16]. Three of the six reviewed studies had fatigue as one of the outcome measures and all three reported a reduction in fatigue [17-19]. However, the methodological quality of these pilot studies was evaluated as poor and only one study had a control condition [16].

Following the NCCN recommendations for exercise programs, our research group developed a 6-week GET intervention that was tailored to the physical fitness level of each participant and began at a low level of intensity and duration, progressed slowly, and was modified when the participant’s condition changed. This intervention was tested for feasibility and efficacy was explored in an uncontrolled pilot study of 26 incurable cancer patients. GET was not only feasible in terms of participants’ adherence and evaluation, but also efficacious with significant improvements in self-reported fatigue and quality of life [20]. A large-scale randomised controlled trial (RCT) is needed to confirm these promising results.

Cognitive Behaviour Therapy for CRF in cancer patients

Most research on the efficacy of CBT for CRF has been done in cancer survivors or cancer patients receiving cancer treatment with curative intent. Systematic reviews and meta-analyses have indicated that CBT can reduce fatigue in cancer survivors [21, 22]. Two RCTs performed by our research group have demonstrated that fatigue and functional impairments in severely fatigued cancer survivors can be significantly reduced by CBT for CRF [23, 24]. This fatigue-specific intervention targets several cognitive-behavioural perpetuating factors of CRF. The intervention is based on the underlying assumption that cancer treatment and/or the cancer itself may trigger fatigue (precipitating factors), but that other factors such as sleep disturbance,
physical inactivity, and dysfunctional thoughts about fatigue might be responsible for the persistence of fatigue (perpetuating factors) [25]. Positive intervention effects of CBT for CRF were sustained at 2-years follow-up [26]. The efficacy of CBT for CRF compared to usual care was also assessed in an RCT aimed at cancer patients during cancer treatment with curative intent [27]. Despite a significant reduction in fatigue immediately after the intervention for patients in the CBT arm, no differences were observed between these two conditions at follow-up with effects diminishing after seven months [28]. It should be noted though, that being severely fatigued was not an entry criterion for this RCT, and thus a floor effect may be present in this trial.

While there are no RCTs to date that investigated the efficacy of CBT specifically aimed at reducing fatigue in incurable cancer patients receiving cancer treatment with palliative intent, two previous RCTs provide indirect support for the positive effects of CBT on fatigue outcomes in a sample of cancer patients of whom a subgroup had incurable cancer [29, 30]. Although these RCTs did show an overall effect on fatigue, it is not clear whether this can be generalised to the group of cancer patients receiving treatment with palliative intent since subgroup analyses were not performed. Based on our previous experience with CBT for CRF in both cancer survivors and patients receiving cancer treatment with curative intent, and results of a recent study which suggested that the same perpetuating psychosocial factors are associated with fatigue in patients receiving cancer treatment with palliative intent [12], we think it is important to examine the efficacy of CBT for CRF in an RCT for this new target population.

The role of physical activity and fitness versus fatigue-related cognitions as mediators of the reduction in CRF

Exercise interventions aiming to reduce CRF in cancer patients are based on the assumption that a lack of physical activity and deconditioning during cancer treatment can worsen fatigue [31]. It is assumed that with exercise interventions physical activity and fitness can be increased, resulting in a reduction in CRF. CBT aimed at reducing CRF in cancer patients is based on the assumption that several fatigue-related cognitions (i.e. low self-efficacy and catastrophising thoughts) and behaviours are related to the persistence of fatigue [25]. Targeting cognitions with CBT is assumed to result in less dysfunctional thoughts about fatigue, which contributes to the reduction in CRF. Although these assumptions are widespread, the role of an increase in physical activity and fitness versus a change in fatigue-related cognitions in reducing CRF has not yet been investigated in interventions for patients with incurable cancer. To investigate which factors contribute to a reduction in CRF, mediation analysis can be helpful. This technique provides insight into which factors mediate the expected reduction in CRF brought on by GET and CBT. Mediation analysis can thereby help us to better understand how interventions work [32].
Aims of the TIRED study
We designed a multicentre RCT to test the efficacy of either GET or CBT compared to Usual Care (UC) in reducing fatigue (primary outcome) in incurable cancer patients receiving systemic treatment with palliative intent. In addition, the efficacy on improving quality of life and functional impairment will be studied. All outcomes will be assessed at baseline, and at 14, 18 and 26-weeks post-randomisation. We will assess the efficacy of GET or CBT compared to UC directly post-intervention at 14-weeks post-randomisation, which is the primary endpoint of this study. In addition, we will determine whether the expected intervention effects are sustained at follow-up assessments (18-weeks and 26-weeks post-randomisation). Furthermore, if GET and/or CBT are efficacious in reducing CRF, we will perform a mediation analysis to test if the changes in four variables (i.e. physical activity, physical fitness, self-efficacy with respect to fatigue, and/or fatigue catastrophising) mediate the reduction in fatigue.

METHODS

Design
A non-blinded multicentre RCT (the TIRED study) will be conducted to evaluate the efficacy of GET and CBT compared to UC for severely fatigued incurable cancer patients receiving cancer treatment with palliative intent.

Participants
Inclusion and exclusion criteria are listed in Table 1. Patients diagnosed with incurable cancer, receiving systemic treatment with palliative intent, and with a cancer treatment plan based on an expected survival of at least 6 months as judged by their oncologist, will be further assessed for eligibility by nurses and oncologists. We will include patients diagnosed with one of the following cancer types: breast, colorectal, prostate, renal cell, bladder, endometrial, ovarian, cervical, bone and soft tissue, or melanoma. Systemic cancer treatment may include chemotherapy, hormone therapy, targeted therapy, and/or immunotherapy, possibly combined with surgery and/or radiotherapy. The presence of severe fatigue reflected by a score of 35 or higher on the subscale fatigue severity of the Checklist Individual Strength (CIS-fatigue) will be used as a criterion for study entry [33].

Recruitment
Nurses and oncologists working at oncology outpatient clinics of two University-affiliated hospitals and seven Regional hospitals in the Netherlands will recruit patients. Patients will be screened for the presence of severe fatigue as part of clinical care by administering the CIS-fatigue prior to the start or during systemic
treatment with palliative intent when patients visit the outpatient clinic. When eligible patients are severely fatigued, the nurse or oncologist will present the TIRED study by giving patients written information and solicit permission to have a researcher contact them. Those patients who agree to be contacted will be called by the coordinating researcher (HP), who will further inform them about the details and purpose of the study and invite them to participate. A follow-up phone call will be scheduled one week after the first phone call to address questions and determine if patients are willing to participate.

Table 1. Inclusion and exclusion criteria TIRED study

<table>
<thead>
<tr>
<th>INCLUSION CRITERIA</th>
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</thead>
<tbody>
<tr>
<td>(1) Age ≥ 18 years.</td>
</tr>
<tr>
<td>(2) Able to read, speak and write the Dutch language.</td>
</tr>
<tr>
<td>(3) Diagnosis of incurable cancer (i.e. breast, colorectal, prostate, renal cell, bladder, endometrial, ovarian, cervical, bone and soft tissue cancer, or melanoma).</td>
</tr>
<tr>
<td>(4) Scheduled for or receiving systemic cancer treatment with palliative intent (i.e., chemotherapy, and/or hormone therapy, and/or targeted therapy, and/or immunotherapy, possibly combined with surgery and/or radiotherapy).</td>
</tr>
<tr>
<td>(5) Cancer treatment plan based on an expected survival of ≥ 6 months as judged by their oncologist.</td>
</tr>
<tr>
<td>(6) Severely fatigued (CIS-fatigue score ≥ 35).</td>
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</tbody>
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<thead>
<tr>
<th>EXCLUSION CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Treatable somatic cause that could explain the presence of severe fatigue (other than the underlying disease and the cancer treatment itself).</td>
</tr>
<tr>
<td>(2) Karnofsky Performance Status &lt; 70.</td>
</tr>
<tr>
<td>(3) Symptomatic brain metastases.</td>
</tr>
<tr>
<td>(4) Severe cognitive problems.</td>
</tr>
<tr>
<td>(5) Not able to walk at least 6 minutes successively.</td>
</tr>
<tr>
<td>(6) Contra-indication for physical exercise.</td>
</tr>
<tr>
<td>(7) Current treatment by a psychiatrist or psychologist for a psychiatric disorder.</td>
</tr>
</tbody>
</table>

Procedure

Eligible patients willing to participate in the study will be asked to sign informed consent upon which they will be invited by a research assistant to complete the baseline assessment (T0) at their own hospital. Upon completion of T0, the research assistant will use a central web-based randomisation service to randomly allocate a participant to one of the three study arms: (1) GET in addition to UC; (2) CBT in addition to UC; or (3) control group receiving UC (see Figure 1). Participants assigned to GET or CBT will start the intervention approximately two weeks after T0. Both interventions will be delivered at or near their own hospital over a period of 12 weeks. Participants
assigned to CBT will complete a set of additional questionnaires to determine relevant intervention modules prior to the first intervention session. Participants assigned to GET will complete an additional submaximal test to determine physical fitness during the first intervention session. At 14 weeks, participants are invited by the research assistant to complete the post-intervention assessment (T1) at the hospital. Follow-up assessments at 18 weeks (T2) and 26 weeks (T3) are entirely web-based and will be completed at home. For participants that do not have Internet access, a paper version of the follow-up questionnaires will be send to their home address, which can be returned in a self-addressed, pre-stamped envelope.

Figure 1. Flowchart of the TIRED study
Randomisation
A central web-based randomisation service provided by an independent statistician will be used. Randomisation will be stratified by centre. We will use block randomisation to reach the same number of participants in all study arms. The ordering of blocks and their respective size will be unknown for the research assistants and coordinating researcher. When possible, minimisation on gender will be performed in order to balance the gender distribution in all study arms. If block randomisation restricts the choice to two or only one study arm, minimisation will always be overruled by block randomisation. A research assistant will perform allocation upon completion of T0 in the presence of the participant.

Interventions

Graded Exercise Therapy
Participants assigned to the GET group will receive a 12-week supervised exercise programme in addition to UC. The treatment protocol ‘GET for fatigue in incurable cancer patients’ was developed by the study investigators in cooperation with a physiologist (MH) and physical therapist (RN) experienced in exercise programmes for cancer patients. The treatment protocol was based on the protocol for a previous pilot-study in patients with incurable cancer [20]. Physical therapists affiliated with the participating hospitals or from local physical therapy centres will deliver the GET. All therapists will be instructed about the treatment protocol and use of registration forms before enrolment of participants. Throughout the study, supervision will be provided upon request by a physical therapist (RN).

GET will be given by physical therapists individually or in small groups with a maximum of 5 participants, depending on the accrual rate. During the intake session, the physical therapist will collect information about a participant’s physical fitness level (by means of a submaximal test) and physical limitations. Participants will formulate treatment goals in activities of daily living together with the physical therapist, such as performing activities or leisure interests in the foreseeable future that are currently difficult to perform because of a lack of muscle strength or cardiopulmonary fitness. After the intake session, participants will receive weekly two-hour sessions of individually graded training supported by a physical therapist and adjusted to their abilities. In order to adjust the training to an individual participant, their heart rate reserve (HRR) and muscle strength (by means of one-repetition maximum [1RM] tests) will be determined during first session and after every three sessions. The two-hour GET sessions will include a warming up (10 min), high intensity aerobic interval training (35 min), a break (15 min), resistance training (35 min), and a cooling down (10 min). Additionally, there are 15 minutes available for evaluation of the GET session. In addition to this supervised session, participants are offered to practise in a second weekly session. After every three sessions, training progress will be evaluated and
the programme will be adjusted by means of the newly determined HRR and 1RM and discussion of formulated treatment goals.

**Aerobic training.** The aerobic training will consist of cycling on an interval basis prior to the resistance training. Intervals will include alternated bicycling for four minutes at 60% (increasing to 80%) of participants’ HRR with three minutes on 35% (increasing to 50%) of HRR. Heart rate will be monitored during the aerobic training using a Polar® breast band (Polar T31 Breast Band, 2008, Polar Electro, Finland). We will use the Borg Scale of Perceived Exertion after each cycling interval to gauge the perceived intensity of the aerobic training [34].

**Resistance training.** The resistance program will include a circuit of seven exercises targeting large muscle groups important for activities of daily living. The following exercises will be executed: (1) leg press; (2) lunge; (3) vertical row; (4) lateral pull down; (5) abdominal crunch; (6) pull over; and (7) bench press. Exercises will be executed at 60-80% of participants’ 1RM and will consist of 3 sets of 8 to 12 repetitions. Some exercises will be performed more often based on the participants’ difficulties in this area and his or her goals in activities of daily living. Progression will be conducted by the graded activity principle, which states that the focus is on successes and positive experiences and that negative experiences will be prevented as much as possible [35].

**Cognitive Behaviour Therapy**
Participants in the CBT group will receive ‘CBT for fatigue in incurable cancer patients’ in addition to UC. This intervention was developed by the study investigators based on the evidence-based protocol of CBT for post-cancer fatigue [23, 26]. Adaptations were done for application with our new target population. This adapted CBT will consist of a maximum of ten sessions over a period of 12 weeks (i.e., one assessment session and maximum nine individual one-hour face-to-face treatment sessions). Qualified and trained psychologists will deliver CBT for fatigue. Prior to intervention delivery, all therapists will receive a three-day training provided by two experienced clinical psychologists (HK and TB). This training will provide background and rationale for each of the intervention modules and involves role-playing to practise the intervention components. An experienced clinical psychologist (HK) will provide on-going supervision to CBT therapists throughout the study.

CBT for fatigue in incurable cancer patients includes several modules aimed at fatigue-perpetuating cognitions and behaviours. Participants randomised to CBT will complete a set of additional questionnaires prior to the first intervention session to assess potential perpetuating factors (see Table 2). During the first intervention session it will be determined by the therapist which factors are applicable for the
particular patient, which leads to a tailored-made intervention as only the relevant treatment modules will be selected. The goal of CBT is reduction of severe fatigue and fatigue-related disability. All participants will start with setting their treatment goals. Participants will be helped to formulate concrete goals in behavioural terms, such as resuming activities or leisure interests in the foreseeable future that are discontinued because of being severely fatigued. Then, therapists and participants will work on adjusting the fatigue-perpetuating factors that are applicable to the individual participant: (1) sleep problems and deregulated sleep-wake cycle; (2) dysfunctional cognitions regarding cancer (prognosis) and cancer treatment; (3) dysfunctional fatigue-related cognitions; (4) deregulated activity pattern; (5) negative social interactions and low perceived social support. Each of these perpetuating factors corresponds to a treatment module:

**Module 1: Regulation of sleep-wake cycle and improving sleep hygiene.** The patient will be explained how the ‘biological clock’ can be reset, in order to establish a consistent sleep-wake pattern with regular bed and wake-up times and no day-time napping. If necessary, advice with respect to sleep hygiene will be given.

**Module 2: Reformulate dysfunctional cognitions regarding cancer and cancer treatment.** This module aims to help the patient formulate more helpful beliefs to improve his or her coping with the fact of having incurable cancer, including fear of the future, and experiencing side effects of cancer treatment. Dysfunctional beliefs will be discussed and restructured.

**Module 3: Reformulate dysfunctional cognitions regarding fatigue.** The goal is to increase self-efficacy with respect to fatigue, reduce fatigue catastrophising, and help the patient to focus less on fatigue.

**Module 4: Regulation of activity.** Two activity patterns will be distinguished on the basis of actigraphy (see ‘Outcomes’): relatively active or low active. Some severely fatigued patients have a persistent low level of physical activity, while others have a more fluctuating activity pattern with bursts of activities followed by periods of inactivity (‘all-or-nothing behaviour’). Both activity patterns can perpetuate fatigue. Relatively active participants are helped to spread their physical, mental, and social activities more evenly over the day and week. Subsequently, participants will gradually increase their physical activity level by means of a daily walking or cycling program of their choice. The chosen activity will be gradually and systematically increased. Low active participants will be motivated to immediately start with the graded activity program. By increasing physical activity, participants’ self-efficacy with respect to physical activity and fatigue will often change positively. Eventually, participants will also increase mental and social activities.
Table 2. Instruments to assess which CBT modules are indicated

<table>
<thead>
<tr>
<th>CBT MODULE</th>
<th>INSTRUMENT</th>
<th>RATING (RANGE)</th>
<th>CUT-OFF VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep problems and deregulated sleep-wake cycle</td>
<td>Sleep-wake diary</td>
<td>Bedtimes and wake up times of 12 consecutive days and nights</td>
<td>Visual inspection of bedtimes and wake up times</td>
</tr>
<tr>
<td></td>
<td>Sickness Impact Profile [41]: subscale Sleep and Rest</td>
<td>Number and type of items endorsed, weighted according to a standardised weighting scheme</td>
<td>Score ≥ 60</td>
</tr>
<tr>
<td></td>
<td>Symptom Checklist-90 [52]: subscale Sleeping Problems</td>
<td>5-point Likert scale (3-15)</td>
<td>Score ≥ 6</td>
</tr>
<tr>
<td>Dysfunctional cognitions regarding cancer (prognosis) and cancer treatment</td>
<td>Impact of Event Scale [53]: subscale Intrusion</td>
<td>4-point Likert scale (7-28)</td>
<td>Score ≥ 10</td>
</tr>
<tr>
<td></td>
<td>subscale Avoidance</td>
<td>4-point Likert scale (8-32)</td>
<td>Score ≥ 10</td>
</tr>
<tr>
<td></td>
<td>Pictorial Representation of Illness and Self Measure [54]</td>
<td>Self-illness separation (SIS) in cm</td>
<td>Fatigue-related suffering: SIS &gt; SFS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Self-fatigue separation (SFS) in cm</td>
<td>Illness-related suffering: SFS &gt; SIS</td>
</tr>
<tr>
<td></td>
<td>Illness Cognition Questionnaire [55, 56]: subscale Acceptance</td>
<td>4-point Likert scale (6-24)</td>
<td>Score ≤ 12</td>
</tr>
<tr>
<td></td>
<td>subscale Helplessness</td>
<td>4-point Likert scale (6-24)</td>
<td>Score &gt; 14</td>
</tr>
<tr>
<td></td>
<td>Beck Depression Inventory-II Primary Care [57]</td>
<td>4-point Likert scale (0-21)</td>
<td>Score ≥ 4</td>
</tr>
<tr>
<td></td>
<td>Hospital Anxiety and Depression Scale [58]: subscale Anxiety</td>
<td>4-point Likert scale (0-21)</td>
<td>Score ≥ 9</td>
</tr>
<tr>
<td></td>
<td>subscale Depression</td>
<td>4-point Likert scale (0-21)</td>
<td>Score ≥ 9</td>
</tr>
<tr>
<td>Dysfunctional fatigue-related cognitions</td>
<td>Fatigue Catastrophising Scale [45]</td>
<td>5-point Likert scale (10-50)</td>
<td>Score ≥ 16</td>
</tr>
<tr>
<td></td>
<td>Self-Efficacy Scale [26, 59]</td>
<td>4-point Likert scale (7-28)</td>
<td>Score ≤ 19</td>
</tr>
<tr>
<td></td>
<td>Illness Management Questionnaire-factor III [60]</td>
<td>6-point Likert scale (9-54)</td>
<td>Score ≥ 30</td>
</tr>
<tr>
<td></td>
<td>Anxiety for Fatigue</td>
<td>4-point Likert scale (8-32)</td>
<td>Score ≥ 14</td>
</tr>
<tr>
<td>Deregulated activity pattern</td>
<td>Actigraphy during 12 consecutive days</td>
<td>Number of days with a mean physical activity level &gt; 66</td>
<td>Low-active: 0-1 Relatively-active: ≥ 2</td>
</tr>
<tr>
<td></td>
<td>Sickness Impact Profile [41]: subscale Social Interactions</td>
<td>Number and type of items endorsed, weighted according to a standardised weighting scheme</td>
<td>Score ≥ 10</td>
</tr>
<tr>
<td></td>
<td>Checklist Individual Strength [33]: subscale Concentration</td>
<td>7-point Likert scale (5-35)</td>
<td>Score ≥ 18</td>
</tr>
<tr>
<td>Negative social interactions and low perceived social support</td>
<td>Van Sonderen Social Support Inventory [61] (shortened version): subscale Negative Interactions</td>
<td>4-point Likert scale (7-28)</td>
<td>Score ≥ 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>subscale Discrepancies</td>
<td>Score ≥ 14</td>
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</tbody>
</table>
Module 5: Improve social support and change unhelpful social expectations. This module is directed at modifying the patients' unhelpful cognitions regarding their social environment, as they can maintain fatigue. Unrealistic expectations towards others are detected and disputed. Patients will practise with exercises in order to change these unhelpful cognitions and are encouraged to involve their partner in this module. Also, coping strategies in contact with others, such as family, friends, and/ or colleagues, will be discussed.

After addressing the perpetuating factors of fatigue, patients will gradually work towards realising the treatment goals formulated at the start of the intervention. At the end of the intervention it is discussed how to deal with new episodes of fatigue, that may be induced when starting further lines of systemic cancer treatment.

Usual care and use of co-intervention
All participants will be treated for incurable cancer in concordance with national and regional cancer clinical practice guidelines of the Dutch Comprehensive Cancer Centres [36]. Participants assigned to the control group have no access to one of the two study interventions, but may be referred by their oncologist or general practitioner to physical therapists or psychologists as part of UC. Participants assigned to CBT will be asked not to follow an exercise programme as part of UC simultaneously, and participants assigned to GET will be asked not to follow a psychological intervention as part of UC simultaneously. We will collect information on whether participants have engaged in exercise programmes or psychological interventions as part of UC at all three post-randomisation assessments (T1, T2, and T3).

Adverse events
All adverse events (AEs) and serious adverse events (SAEs) reported spontaneously by the participants or observed by the GET or CBT therapists will be recorded. All reported AEs will be followed until they have aborted, or until a stable situation has been reached. SAEs are defined as any medical occurrence that results in death, is life threatening, requires hospitalisation, results in persistent or significant disability or incapacity, or a new event of the study likely to affect the safety of participants. SAEs will be reported to the Research Ethics Committee of the University-affiliated hospital that approved the study protocol. At post-intervention assessment (T1), patients will be asked whether they think they currently experience or have experienced AEs as a result of the intervention (GET or CBT) they have received. In case of an affirmative answer, patients will be asked to specify these AEs.
Adherence and treatment integrity
Data will be collected with respect to participants' attendance of GET or CBT sessions, dropout from the intervention (< 2 sessions attended), and therapists' adherence to the protocol. Adherence to GET and CBT intervention protocols will be determined by means of evaluating the registration forms completed by therapists, including components of the intervention protocol that have been addressed during each session. In addition, with permission of participants, all CBT sessions will be audio taped and upon study completion a random sample of 5% will be analysed to determine treatment integrity.

Refusal of study participation and study dropout
The researcher will record the reasons why patients do not participate, why participants dropout from the intervention, and why study assessments are not completed (T1, T2, or T3). Upon completion of the study, these reasons will be categorised, scored and analysed to gain insight into the generalisability of the findings.

Outcomes
Outcome measures and data collection time points are listed in Table 3. The primary endpoint of this study is the post-intervention assessment (T1), 14 weeks after randomisation. Primary and secondary outcomes will be measured at baseline (T0), post-intervention (T1) and follow-up (T2, T3). Proposed mediators will only be assessed at T0 and T1.

Primary outcome
Fatigue severity will be measured using the subscale fatigue severity (8 items, 7-point Likert scale) of the Checklist Individual Strength (CIS-fatigue) [37]. Scores range from 8 to 56. A score of 35 points or higher is an indication for severe fatigue. The CIS-fatigue has been used in previous intervention studies aimed at CRF and proved to be sensitive to change [23, 27]. The CIS-fatigue has good reliability (Cronbach’s alpha = 0.88) and discriminative validity [33].

Secondary outcomes
Fatigue will also be assessed with the symptom scale fatigue (3 items, 4-point Likert scale) of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30, version 3.0). The EORTC QLQ-C30 is developed for use in clinical trials in cancer patients [38]. This instrument consists of five functional and three symptom scales in addition to a scale on global health related quality of life (HRQoL), and a number of single items assessing additional symptoms [38, 39]. Total scores on each subscale are linearly converted to a 0 to 100 scale. Higher scores represent more fatigue.
Table 3. Data collection time point of all outcome measures and proposed mediators

<table>
<thead>
<tr>
<th>CONCEPT</th>
<th>QUESTIONNAIRE</th>
<th>MEASUREMENT TIME POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>T0</td>
</tr>
<tr>
<td>Socio-demographics</td>
<td>Self-report questionnaire</td>
<td>X</td>
</tr>
<tr>
<td>Medical characteristics</td>
<td>Medical chart review</td>
<td>X</td>
</tr>
<tr>
<td>Primary outcome:</td>
<td></td>
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<tr>
<td>Fatigue severity</td>
<td>CIS fatigue severity</td>
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<tr>
<td>Secondary outcomes:</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fatigue</td>
<td>EORTC QLQ-C30 fatigue</td>
<td>X</td>
</tr>
<tr>
<td>Quality of life</td>
<td>EORTC QLQ-C30 global health status</td>
<td>X</td>
</tr>
<tr>
<td>Functional impairments</td>
<td>SIP</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>EORTC QLQ-C30 emotional functioning</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>EORTC QLQ-C30 physical functioning</td>
<td>X</td>
</tr>
<tr>
<td>Proposed mediators:</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Actigraphy during 12 consecutive days</td>
<td>X</td>
</tr>
<tr>
<td>Physical fitness</td>
<td>6MWT</td>
<td>X</td>
</tr>
<tr>
<td>Self-efficacy</td>
<td>SES</td>
<td>X</td>
</tr>
<tr>
<td>Fatigue catastrophizing</td>
<td>FCS</td>
<td>X</td>
</tr>
</tbody>
</table>

T0 = baseline (pre-intervention); T1 = post-intervention/UC (14 weeks post-randomisation); T2 = first follow-up assessment (18-weeks post-randomisation); T3 = second follow-up assessment (26-weeks post-randomisation).

The subscale global health status/QoL (2 items, 7-point Likert Scale) of the EORTC QLQ-C30 will be used to measure quality of life. A high score indicates good HRQoL. The EORTC QLQ-C30 is one of the most commonly used HRQoL instruments [40] and is known to be a reliable and valid measure of the quality of life of cancer patients [38].

Functional impairments will be assessed with two instruments. We will include seven subscales of the Sickness Impact Profile (SIP) to assess the level of functional impairments [41]. This questionnaire measures the influence of complaints in different areas of daily functioning. The following subscales will be used: alertness behaviour, sleep, homemaking, leisure activities, mobility, social interactions, and ambulation. High scores reflect high levels of functional impairments. The SIP is known to be a reliable instrument with sufficient content validity [42]. In addition to the SIP, functional impairments will also be assessed by the subscales emotional functioning (4 items, 4-point Likert scale) and physical functioning (5 items, 4-point Likert scale) of the EORTC QLQ-C30. Raw scores for both subscales are convertible to a score of 0 to 100. A high score represents a high level of functioning.
Proposed mediators
Change scores (T1-T0) for each proposed mediator will be calculated and used for multiple mediation analysis. The following proposed mediators will be assessed at T0 and T1.

Physical activity. The level of physical activity will be assessed with actigraphy. Participants will be wearing an actometer around the ankle for twelve consecutive days and nights following T0 and T1. This actometer is a motion-sensing device based on a piezo-electric sensor recording the number of movement at five-minute intervals and with highly reproducible readings [43]. The mean daily physical activity score over twelve days can be calculated as a measure of physical activity.

Physical fitness. We will assess the level of physical fitness with the Six-Minute Walk Test (6-MWT). This is an easy to perform and practical submaximal exercise test that has been increasingly used across various patient populations. The 6-MWT will be conducted in an indoor corridor on a pre-measured test-course of 20 meters. Participants will be instructed to walk from one end to the other while attempting to cover as much distance as possible during the allotted time. Patients who normally use walking aids will be allowed to use them during the test. The total walking distance covered in six minutes provides an indirect measure of aerobic functional fitness [44].

Self-efficacy with respect to fatigue. The seven-item self-efficacy scale (SES) will be used to measure the amount of experienced control over fatigue [26]. All items are scored on a 4-point Likert scale. Higher scores are indicative for more sense of control.

Fatigue catastrophising. We will use the ten-item Fatigue Catastrophizing Scale to measure catastrophising in response to fatigue [45]. All items are scored on a 5-point Likert scale. Higher total scores indicate more fatigue catastrophising.

Sample size calculation
Based on the primary outcome measure of the TIRED study, efficacy of one or both interventions is demonstrated when mean fatigue severity (CIS-fatigue) in participants assigned to GET and/or CBT is significantly lower at T1 compared to participants assigned to UC. A clinically relevant difference between the intervention arms and the UC arm of at least 6 points is expected for the primary outcome (CIS-fatigue). Per arm, a minimum number of 51 evaluable participants at T1 would be needed for a $t$-test with a power of 0.80 and a two-sided alpha of 0.025 (corrected to account for the two comparisons: GET versus UC and CBT versus UC). According to Borm et al. (2007) [46], using analysis of covariance (ANCOVA) instead of a $t$-test to analyse treatment effects on a continuous outcome measure (CIS-fatigue) increases the
power and reduces the needed sample size in RCTs. This proposed ‘design factor’ for ANCOVA can be calculated by multiplying the number of participants needed for the t-test by $1 - p^2$, where $p$ is the correlation between the outcome measure at T0 and T1. Since no data on the correlation of the CIS-fatigue from earlier trials in this particular patient group were available, we used a conservative approach by assuming a weak correlation ($1 - 0.10^2 = 0.99$) and thus the number of participants needed was not reduced. Anticipating an attrition rate of 30%, we aim to recruit a target sample size of 219 participants at T0 (73 participants per arm).

**Statistical analyses**

The statistician who will perform data analyses will be blinded for intervention allocation. To test the efficacy of both interventions compared to UC, an ANCOVA will be performed for each intervention with fatigue severity (CIS-fatigue) at T1 as dependent measure, condition as fixed factor and CIS-fatigue screening score as covariate [47]. Missing data is a common problem in palliative care research and is also anticipated in our study as a result of deteriorating health or because the patient has died. Data will be primarily analysed on complete case basis, i.e. only data from evaluable participants with a T1 assessment will be used. The $p$-level is adjusted to 0.025 to account for the two primary analyses, i.e. GET versus UC and CBT versus UC. When statistically significant differences between GET versus UC and/or CBT versus UC are found, additional sensitivity analysis accounting for all randomised participants will be done to explore the impact of missing data. Several methods of imputation are available and the choice will depend on the actual circumstances of missing data. We will record the causes of missing data and careful considerations will be given to which imputation procedure should be used.

In addition, ANCOVA will be performed for the secondary outcomes (fatigue, quality of life, and functional impairments), with baseline score (T0) on the dependent measure as covariate. In these exploratory analyses a $p$-level of 0.05 will be used. Longer-term follow-up effects at T2 and T3 will also be tested using ANCOVA, with baseline score (T0) on the dependent measure as covariate. Again, in these explorative analyses a $p$-level of 0.05 will be used. No sensitivity analysis will be done, as the power for follow-up analyses will be limited due to the expected significant amount of attrition.

Mediation analysis will be conducted to explore the possible underlying mechanisms of the expected reduction in fatigue severity (CIS-fatigue) brought on by GET and CBT at T1. Following recommendations of Preacher and Hayes (2008) [48], we will perform multiple mediation analysis using bootstrapping to test the mediating effect of four potential mediators (i.e. changes in physical activity, physical fitness, self-efficacy with respect to fatigue, and catastrophising in response to fatigue). We will only perform multiple mediation analysis when there is a significant effect of one or both interventions compared to UC.
Ethical approval

The study protocol has been reviewed and approved by the Research Ethics Committee of our University-affiliated hospital (CMO Arnhem-Nijmegen, reference no. 2012/240) and the local Ethics Committees of the participating hospitals (Hospital Gelderse Vallei, Máxima Medical Center, Isala Hospital, Canisius-Wilhelmina Hospital, Hospital Pantein, Jeroen Bosch Hospital, VieCuri Medical Center, and Academic Medical Center). The study is registered in the Dutch Trial Registry (reference no. NTR3812, date registered: January 23, 2013).

DISCUSSION

Fatigue is one of the most prevalent symptoms compromising quality of life of incurable cancer patients receiving systemic treatment with palliative intent. Graded exercise and cognitive behavioural interventions seem promising in reducing fatigue severity based on their effectiveness in disease-free cancer patients and patients receiving cancer treatment with curative intent. To our knowledge, the TIRED study will be the first RCT determining the efficacy of GET and CBT compared to UC in reducing severe fatigue in incurable cancer patients receiving systemic treatment with palliative intent.

Recruitment of participants started in January 2013. Thus far, identifying potential study participants via nurses and oncologists for this palliative care RCT has been challenging. One common barrier for recruitment in palliative care research known from the literature is professional gatekeeping [49]. A recent systematic review by Kars et al. (2015) explored reasons for gatekeeping in palliative care research, the professionals’ perception that study participation would be too burdensome for the patients was the most reported reason [50]. Yet, we recently demonstrated that 93% of incurable cancer patients that completed a fatigue-screening questionnaire during cancer treatment with palliative intent wanted to be informed by a researcher about available interventional studies for fatigue [51]. Other important reasons for gatekeeping reported by Kars et al. (2015) included health carers’ lack of time, complicated study procedures, or study procedures that interrupt usual care processes [50]. These issues have also been observed in our study and as a result we have simplified our study procedures. For example, we originally aimed to screen for the presence of severe fatigue during a nursing consultation before the first line of systemic treatment with palliative intent began. However, nurses indicated that patients often raise several important time-consuming treatment-related questions, which hampered nurses from administering the fatigue screening. Therefore, we amended the study protocol by also allowing patients to be screened for fatigue at consultations further on during treatment. Moreover, we initially aimed to include a
homogeneous sample of patients with incurable breast or colorectal cancer. Then again, poor recruitment rates during the first year made us broaden our inclusion criterion regarding cancer type. Finally, we have extended our research collaboration with three hospitals to nine hospitals in total. All study protocol amendments have been reviewed and approved by the Research Ethics Committee of our University-affiliated hospital and the local Ethics Committees of the participating hospitals.

In conclusion, the TIRED study will provide information on the efficacy of GET and CBT compared to UC in reducing severe fatigue in incurable cancer patients, as well as on the mediators of any observed intervention effects. Other important outcome measures will include quality of life and functional impairments. If proven efficacious, one or both interventions might be offered as part of UC for this often overlooked and understudied patient group.
REFERENCES

46. Van Breukelen GJ. ANCOVA versus change from baseline: more power in randomized studies, more bias in nonrandomized studies [corrected]. *J Clin Epidemiol*. 2006;59:920-5.


CHAPTER 8

TIME TO PRACTICE WHAT WE PREACH?
APPRECIATING THE AUTONOMY OF CANCER PATIENTS ON DECIDING WHETHER THEY WANT TO BE INFORMED ABOUT INTERVENTIONAL STUDIES FOR FATIGUE

Hanneke Poort, Marlies Peters, Stans Verhagen, Jopie Verhoeven, Winette van der Graaf, Hans Knoop

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BACKGROUND

Fatigue is a prevalent and burdensome symptom for patients with advanced cancer. The long-term use of pharmacological interventions for fatigue is not supported by evidence [1]; though, non-pharmacological and behavioural interventions are promising approaches to reducing fatigue based on their effectiveness in early-stage cancer patients [2]. Behavioural factors, like sleeping problems and being less physically active, can also contribute to fatigue in advanced cancer patients [3]. Interventional studies for the management of fatigue in advanced cancer patients are needed. However, it is a notorious challenge to identify patients for interventional studies aimed at fatigue or symptom control while patients are undergoing cancer treatment with palliative intent. One of the barriers to successful identification of these patients is professional gatekeeping, due to the care professionals’ perception that study participation might be too burdensome for the patient [4, 5]. Although gatekeeping is done in order to prevent additional burden for patients who are seriously ill, it also limits access for patients to potentially effective interventions for fatigue and makes it difficult to develop evidence-based interventions for fatigue in advanced cancer patients. More importantly, gatekeeping assumes that patients are either not capable to decide for themselves if they want to be informed about an intervention study or do not want to be informed. We aimed to investigate to what extent patients receiving cancer treatment with curative or palliative intent would be willing to be contacted by a researcher about possible interventional studies aimed at fatigue once they were screened for the presence of fatigue in routine clinical practice. An ongoing interventional study addressing fatigue in patients receiving treatment with palliative intent for breast or colon cancer was available at the time of this quality project (TIRED study, Netherlands Trial Registry, NTR3812).

METHODS

At the Radboud university medical center, we conducted a quality project aimed at screening for the presence of severe fatigue in cancer patients prior to starting (a new line of) systemic treatment. Oncology nurses were instructed to introduce the assessment of fatigue to all patients via handing out a pre-printed information letter together with a multi-dimensional fatigue questionnaire. Patients completed the Checklist Individual Strength (CIS) questionnaire directly at the outpatient clinic or at home. The subscale fatigue severity (8 items, 7-point Likert scale) of the CIS was used as a measure of fatigue, a validated cut-off score of ≥ 35 points indicates the presence of severe fatigue [6]. In addition, patients were asked the following question: “Fatigue is an important symptom that influences quality of life during cancer treatment. If this questionnaire shows that fatigue is also an important symptom for you and a treatment is available, do you agree that a researcher contacts you?” Possible answers were ‘yes’ or ‘no’ and in case of an
Appreciating the autonomy of patients with cancer

affirmative answer patients had to provide their contact information. Eligible patients for an ongoing interventional study addressing fatigue in advanced cancer patients receiving treatment with palliative intent for breast or colon cancer were then contacted by a researcher. Oncology nurses provided data on age of the patient, gender, type of cancer, and treatment intent (curative vs. palliative).

RESULTS

A total of 229 patients completed the fatigue-screening questionnaire between January and December 2013. In all, 53% (n=121) were female; mean patient age was 58 years (range 25 to 78). The most common types of cancer were gastro-intestinal cancer (32%) and breast cancer (19%). Other diagnoses included gynecological cancer, skin cancer, head-neck cancer, urogenital cancer, sarcoma, brain tumors, or other. Information about treatment intent was available for 214 patients, 49.5% (n=108) received curative treatment and 50.5% (n=106) received palliative treatment.

In all, 93% (n=212) of patients agreed with being approached by a researcher to be informed about interventional studies for severe fatigue. Of interest, agreement did not differ significantly between patients receiving treatment with curative (91%) versus palliative intent (93%). The prevalence of severe fatigue in patients receiving treatment with palliative intent was 36% (n=38) and 90% (n=34) of those severely fatigued advanced cancer patients agreed to being contacted by a researcher.

CONCLUSIONS

Overall, cancer patients who completed a fatigue-screening questionnaire also wanted to be informed by a researcher about available interventional studies for fatigue, regardless of treatment intent. Even in severely fatigued advanced cancer patients, 90% of patients wanted to be informed. Our findings accord with a survey study performed in advanced cancer patients, in which almost 90% of patients were interested in studies of symptom control, though the concept of randomisation was a deterrent in 40% of patients [7]. In light of the new era of patient participation in health care, advanced cancer patients should not only be involved in decisions about medical treatment, but also in deciding whether they want to be informed about studies targeting symptoms and quality of life. Thus, there is no need for well-meant protection of patients receiving treatment with palliative intent by withholding from them information about fatigue interventional studies. Researchers developing evidence-based interventions for fatigue in advanced cancer patients may use our findings to convince health care professionals to actively refer these patients for information about interventional studies, including randomised controlled trials.
REFERENCES


Appreciating the autonomy of patients with cancer
CHAPTER 9

WHY IS PATIENT RECRUITMENT FOR A FATIGUE INTERVENTIONAL STUDY IN PATIENTS WITH INCURABLE CANCER SO DIFFICULT?
LESSONS LEARNED FROM THE TIRED STUDY

Hanneke Poort, Marlies Peters, Stans Verhagen, Winette van der Graaf, Gijs Bleijenberg, Hans Knoop

Submitted for publication
ABSTRACT

Background
The present study investigated the difficulties in recruitment of patients for a still ongoing three-armed multicentre randomised controlled trial (RCT) comparing a cognitive behavioural or exercise intervention with usual care for severely fatigued patients with incurable cancer.

Methods
Figures on the availability of potential study candidates were derived from two out of the eight participating hospitals. Recruitment rate per hospital was calculated. T-tests and Chi² tests were used to examine differences between participants and non-participants in age, gender, and fatigue. Reasons for non-participation were recorded and other recruitment barriers were discussed in frequent study team meetings.

Results
Based on the estimated number of patients needed for identification and the national cancer incidence and 5-year survival and mortality rates in the Netherlands, we argue that sufficient potential candidates were available for identification. From January 2013 to December 2016, 201 eligible patients were identified. In total, 122 participants were randomised (61%). Doctors and nurses missed potential candidates for identification and screening. The inclusion rate between centres varied largely (2-10 patients/year). Engagement of research nurses proved to be vital in successfully identifying patients. Participants did not differ from non-participants in age (p = .775) or fatigue (p = .719) but male patients were more likely to participate compared to females (p = .01). The primary reason for non-participation was ‘participation perceived as too burdensome’ (n=41; 52%). Both inclusion criteria and study procedures appeared to be too complicated, preventing quick identification of potential candidates by often busy nurses and oncologists.

Conclusion
We identified several difficulties with recruitment for our RCT (doctor and nurse level, patient level, organisational level). Sharing these lessons learned may help other investigators interested in improving patient recruitment in similar palliative or supportive care RCTs.
INTRODUCTION

Patients with incurable cancer experience substantial physical and psychological symptoms that compromise quality of life. The goal of palliative care is to improve the quality of life of patients who have a serious or life-threatening disease by treating as early as possible the symptoms of a disease or the side effects caused by its treatment. Cancer-related fatigue (CRF) is one of the most common symptoms experienced by patients being treated for cancer and is associated with poorer quality of life [1, 2]. Randomised controlled trials (RCTs) are essential to the advancement of intervention research and clinical practice in the area of CRF in patients with incurable cancer. Yet, difficulties in recruitment of sufficient participants into palliative care RCTs have been described before [3, 4] and it continues to be a huge challenge today. A recent Cochrane review investigating the effects of psychosocial interventions for CRF in patients with incurable cancer identified 14 studies involving 3077 randomised patients in total [5, 6]. Eight of the 14 studies had a mixed sample of patients with incurable and potentially curable cancer. The 12 studies included in the subset meta-analysis involved only 535 patients with incurable cancer. The study with the largest sample size randomised 53 and 57 patients to the intervention and control arm, respectively [7]. Problems with recruitment are not unique to palliative care RCTs with psychosocial interventions. Rinck et al. (1997) found that 10 out of 11 studies included in their review on palliative care (excluding sole psychosocial interventions) experienced difficulties with recruitment of participants [8]. In two studies, these difficulties were so severe that the RCTs had to be stopped without achieving the planned sample size [9, 10].

In January 2013, we started patient recruitment for the still ongoing Dutch Cancer Society-funded TIRED study (KUN2011-5259). This RCT is focused on the efficacy of two supportive care interventions (exercise intervention or cognitive-behavioural intervention compared to usual care) in reducing severe CRF in patients with incurable cancer [11]. Due to the disappointing recruitment rate in the first year of the study, we undertook several important actions to improve recruitment. First, we extended our research collaboration from three initial study centres to a total of eight study centres. Second, although we originally intended to collect data from a homogenous study sample of patients diagnosed with incurable breast or colorectal cancer starting first-line systemic therapy, disappointing recruitment rates urged us to include a broader sample of cancer types (i.e. incurable prostate, renal cell, bladder, ovarian, or cervical cancer, and sarcoma or melanoma) and further lines of anticancer therapy. In addition, the recruitment period was intended to last for 33 months, but in December 2016, after 48 months of recruitment and the taken actions, we achieved still only 76% of our recruitment goal. Although we are confident that we will eventually successfully reach our recruitment goal, it is important to share the main barriers and challenges
that we encountered. Lessons learned from our trial could serve future researchers interested in designing and undertaking similar supportive care RCTs within this fragile cancer population. Therefore, the purpose of this paper is not to present an analysis of the effectiveness data since the TIRED study is still ongoing. Instead, we discuss and report on some of the challenges associated with patient identification and recruitment for the trial and provide practical solutions.

There are many reasons why recruitment for RCTs investigating supportive care interventions in patients with incurable cancer is so difficult. First of all, there may not be sufficient potential candidates available for the research study. A well-known phenomenon in clinical trials, known as Lasagna's Law and already described in 1970, states that investigators overestimate the number of patients available for a research study [12]. Also, overly strict inclusion criteria may reduce the number of potential candidates. Therefore, our first aim was to determine whether difficulties in recruitment for our RCT originated from the unavailability of sufficient potential candidates. However, if sufficient potential candidates should be available, several other barriers can still influence recruitment. These barriers can be found at different levels: doctor and nurse level, patient level, and organisational level. For example, doctors and nurses might be reluctant to recruit seriously ill patients for participation in supportive care RCTs based on attitudes of defeatism, other priorities, and limited consultation time. On the other hand, patients might also refuse to participate for various reasons. For example, the efforts and burden for study participants might reduce the motivation of patients to participate. We aimed to explore the barriers and determine whether participants and non-participants differed in specific characteristics such as age or fatigue severity. In addition, our last aim was to determine the reasons for non-participation. It is important to get insight in these barriers and challenges, in order to enable investigators to take these problems into account in designing future trials. This could facilitate recruitment rates, which would help to determine the efficacy of interventions during cancer treatment with palliative intent.

**METHODS**

**TIRED study**
The rationale and design for this trial have been described in detail elsewhere [11]. In short, we aimed to recruit participants diagnosed with incurable cancer (i.e. advanced or metastatic) and reporting clinically significant levels of CRF while on first-line systemic therapy with palliative intent. Doctors and nurses from eight Dutch hospitals initially screen potential study participants to check the eligibility criteria. All eligible patients were contacted by phone by the coordinating researcher (HP) who explained study procedures and invited patients to participate. Eligible patients
willing to participate are randomised to one of three study arms including two intervention arms (cognitive behaviour therapy; CBT or graded exercise therapy; GET) and a control arm (usual care). Participants randomised to one of the two intervention arms receive 12 weeks of weekly CBT or GET in addition to usual care. Sample size was estimated to be 51 evaluable patients in each arm at post-intervention; that is, recruitment should be continued until we reached a sample size of 219 participants, taking an expected attrition rate of 30% into account. Our recruitment period was originally planned between January 2013 and September 2015 (33 months). Doctors and nurses received a financial compensation of €50 per enrolled patient. The Medical Ethics Committees of all participating centres granted approval to conduct the study. Written informed consent was obtained from all participants.

Data and methods of present analysis
Data collected on identification and recruitment of participants from the opening of the trial in January 2013 until December 2016 are presented in this paper. During this period, the study team met weekly to monitor patient recruitment, discuss barriers and challenges, as well as propose, test, and evaluate interventions to overcome these difficulties.

In two hospitals, research nurses were involved in the study and recorded data regarding identification and screening of all potential candidates during 31 months (Hospital A) and 12 months (Hospital G), respectively. Data collected in these two example periods enabled us retrospectively examine whether sufficient potential candidates were available by estimating how many patients needed to be available in order to recruit our target sample size. This estimate was put into perspective using data from the Netherlands Cancer Registry on the national incidence (2012-2015) and 5-year survival and mortality rates (2008-2012) of our selected cancers (all disease stages) (http://www.dutchcancerfigures.nl).

We used process data collected by the coordinating researcher (HP) to describe the recruitment rate per study centre. A description of the main barriers and challenges involved in the study was based on information from progress reports and minutes of the study team meetings. We categorised these barriers into three levels: doctor and nurse level, patient level, and organisational level.

Baseline data provided by potential study participants were used and included age, gender, and fatigue severity. Fatigue severity was assessed with the fatigue severity subscale of the Checklist Individual Strength (CIS-fatigue). The CIS-fatigue consists of 8 items scored on a 7-point Likert Scale. Total scores range between 8 and 56, and a score of ≥ 35 is considered to be an indication of the presence of severe CRF [13]. Descriptive statistics were used to characterize the sample. Independent samples
t-tests and Chi² tests were used to examine differences between participants and non-participants in age, gender, and fatigue severity.

The coordinating researcher (HP) scheduled a follow-up phone call with eligible patients one week after informing them about the study. Free text was used to document the reasons why eligible patients did not wish to participate. These reasons were sorted into one of 5 categories: (1) too much distance to study centre and/or the need for travel arrangements; (2) study participation too burdensome; (3) disliked the aspect of randomisation (because they preferred a particular intervention or UC); (4) not or no longer interested in study participation; or (5) no reasons given.

RESULTS

Availability of potential candidates during the study period
From January 2013 to December 2016, 201 eligible patients were identified by nurses and doctors and contacted by the coordinating researcher to participate in the TIRED study. In total, 122 participants were randomised (61% participation rate). Originally, we envisioned enrolling an average of 6-7 participants per month from three study centres resulting in a recruitment period of 33 months. Instead, we enrolled an average of only 2-3 participants per month from eight study centres in a recruitment period of 48 months. Fortunately, attrition was much lower than anticipated (5% instead of 30%), which allowed us to adjust our required sample size from 219 to 161 participants.

Figure 1 displays a detailed flowchart for patient identification during a 12-month example period at the primary study centre. During the example period at Hospital A, a total of 278 patients were identified for screening of which 9 patients were eventually randomised (3%). In Hospital G, a total of 160 patients were identified for screening during a period of 31 months of which 27 patients were eventually randomised (17%). Based on this example, an estimated 954 to 4973 patients needed to be available for identification to eventually randomise the adapted sample size of 161 participants (i.e. (161/27)*160 and (161/9)*278, respectively).

The national incidence of our selected cancers (all disease stages) between January 2012 and December 2015 was n=213,054 (see Table 1A). Assuming an average mortality of 32% of patients with our selected cancers (± n=68,177, see Table 1B), we would still have enough potential candidates available in the eight participating hospitals (i.e. ± n=5993) out of a total of 91 hospitals in the Netherlands.
Lessons learned from the TIRED study

Figure 1. Flowchart of a 12-month patient identification and recruitment period for the TIRED study (November 2015 to October 2016, Radboudumc)
Table 1A. National incidence per selected cancer type per year from January 2012 until December 2015

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>13.239</td>
<td>13.136</td>
<td>15.166</td>
<td>15.549</td>
<td>57.090</td>
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<tr>
<td>Prostate</td>
<td>11.294</td>
<td>10.977</td>
<td>9.986</td>
<td>10.497</td>
<td>42.754</td>
</tr>
<tr>
<td>Melanoma (skin)</td>
<td>5.316</td>
<td>5.566</td>
<td>5.642</td>
<td>5.926</td>
<td>22.450</td>
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<tr>
<td>Bladder</td>
<td>2.991</td>
<td>2.946</td>
<td>3.001</td>
<td>3.135</td>
<td>12.073</td>
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<td>Renal</td>
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<td>2.327</td>
<td>2.323</td>
<td>2.343</td>
<td>9.237</td>
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<tr>
<td>Ovarian</td>
<td>1.302</td>
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<td>1.260</td>
<td>1.259</td>
<td>5.091</td>
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<td>Cervix</td>
<td>0.731</td>
<td>0.658</td>
<td>0.729</td>
<td>0.715</td>
<td>2.833</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>0.871</td>
<td>0.767</td>
<td>0.866</td>
<td>0.947</td>
<td>3.451</td>
</tr>
<tr>
<td>Total</td>
<td>54.338</td>
<td>54.154</td>
<td>55.707</td>
<td>56.909</td>
<td>213.054</td>
</tr>
</tbody>
</table>

Table 1B. National 5-year survival and mortality per selected cancer type from January 2008 until December 2012

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Survival</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>87%</td>
<td>13%</td>
</tr>
<tr>
<td>Colorectal</td>
<td>63%</td>
<td>37%</td>
</tr>
<tr>
<td>Prostate</td>
<td>88%</td>
<td>12%</td>
</tr>
<tr>
<td>Melanoma (skin)</td>
<td>89%</td>
<td>11%</td>
</tr>
<tr>
<td>Bladder</td>
<td>53%</td>
<td>47%</td>
</tr>
<tr>
<td>Renal</td>
<td>63%</td>
<td>37%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>38%</td>
<td>62%</td>
</tr>
<tr>
<td>Cervix</td>
<td>66%</td>
<td>34%</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>63%</td>
<td>37%</td>
</tr>
<tr>
<td>Average</td>
<td>68%</td>
<td>32%</td>
</tr>
</tbody>
</table>

Main barriers and challenges associated with patient identification and recruitment

Doctor and nurse level

Given the calculation presented in the previous section, doctors and nurses must have missed patients for identification and screening. Despite the acknowledged importance of intervention research for CRF in patients with incurable cancer and initial enthusiasm of doctors and nurses, we experienced several barriers at this level shortly after initiating the study. First, doctors and nurses had limited time available in medical consultations and as CRF was neither the primary goal nor the expertise of the oncology team it often
hampered them from discussing the study. Second, we compensated efforts of the health care research team on a fee-for-performance basis (i.e. €50 per enrolled patient). In retrospect, in spite of intrinsic motivation of doctors and nurses, this compensation model cannot compete with the compensation for studies led by pharmaceutical companies. Third, unawareness of the study despite frequent didactic activities (including presentations and newsletters) and forgetfulness in discussing available studies with patients was observed in doctors and nurses from all study centres.

There was a large variation in the inclusion rate between the eight participating centres ranging from an average inclusion of 2 to 10 participants per year (Table 2). The two hospitals with the highest inclusion rate per month (Hospital A: 10.45 p/y and Hospital G: 7.08 p/y) were the two study centres where we could engage research nurses in patient identification for the study. In the other centres there were no research nurses available for our study. We learned that these dedicated research nurses played a vital role in identifying and screening patients. Together, these two centres contributed to half of our current study sample, accounting respectively for 28% ($n=34$; Hospital A) and 22% ($n=27$; Hospital G) of our total recruitment.

Table 2. Recruitment per study centre between January 2013 and December 2016

<table>
<thead>
<tr>
<th>Study centre</th>
<th>Start of recruitment</th>
<th>Recruitment period</th>
<th>Total inclusion</th>
<th>Average inclusion rate</th>
<th>Total no. of beds$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital A</td>
<td>Jan, 2013</td>
<td>48 mos.</td>
<td>34</td>
<td>7.08 p/y</td>
<td>953</td>
</tr>
<tr>
<td>Hospital B</td>
<td>May, 2013</td>
<td>44 mos.</td>
<td>11</td>
<td>3.00 p/y</td>
<td>510</td>
</tr>
<tr>
<td>Hospital C</td>
<td>June, 2013</td>
<td>43 mos.</td>
<td>11</td>
<td>3.07 p/y</td>
<td>543</td>
</tr>
<tr>
<td>Hospital D</td>
<td>July, 2013</td>
<td>42 mos.</td>
<td>17</td>
<td>4.86 p/y</td>
<td>663</td>
</tr>
<tr>
<td>Hospital E</td>
<td>Oct, 2013</td>
<td>39 mos.</td>
<td>7</td>
<td>2.15 p/y</td>
<td>715</td>
</tr>
<tr>
<td>Hospital F</td>
<td>Nov, 2013</td>
<td>38 mos.</td>
<td>11</td>
<td>3.47 p/y</td>
<td>994</td>
</tr>
<tr>
<td>Hospital G</td>
<td>June, 2014</td>
<td>31 mos.</td>
<td>27</td>
<td>10.45 p/y</td>
<td>474</td>
</tr>
<tr>
<td>Hospital H</td>
<td>June, 2014</td>
<td>31 mos.</td>
<td>4</td>
<td>1.55 p/y</td>
<td>190</td>
</tr>
<tr>
<td></td>
<td></td>
<td>316 mos.</td>
<td>122</td>
<td></td>
<td>5042</td>
</tr>
</tbody>
</table>

Table 3. Characteristics participants and non-participants (n=201)

<table>
<thead>
<tr>
<th></th>
<th>Participants</th>
<th>Non-participants</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=122, 61%)</td>
<td>(n=79, 39%)</td>
<td></td>
</tr>
<tr>
<td>Age (yr.), mean (SD)</td>
<td>63.03 (9.19)</td>
<td>62.61 (10.65)</td>
<td>.775</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n female (%)</td>
<td>70 (57%)</td>
<td>59 (75%)</td>
<td>.01</td>
</tr>
<tr>
<td>n male (%)</td>
<td>53 (43%)</td>
<td>20 (25%)</td>
<td></td>
</tr>
<tr>
<td>CIS fatigue a</td>
<td>45.71 (6.71)</td>
<td>45.34 (6.36)</td>
<td>.719</td>
</tr>
</tbody>
</table>

a Information available for n=195 patients. b Information available for n=181 patients.

**Patient level**

Table 3 shows the characteristics of participants and non-participants from the identified patient group fulfilling the inclusion criteria. Participants did not differ significantly from non-participants in age (p = .775) or fatigue severity score (p = .719). However, male patients were significantly more likely to participate compared to females (p = .01). Table 4 lists the reasons for non-participation. The three most frequently reported reasons for non-participation were (1) study participation too burdensome (52%); (2) not or no longer interested in study participation (22%); and (3) too much distance between patients' home and the study centre and the need for associated travel arrangements (15%). Non-participants refusing because of the latter reason often indicated that they would be willing to participate if they could receive the study intervention closer to their homes. This would enable them to participate without the burden of additional hospital visits and travel arrangements.

Table 4. Reasons for non-participation (n=79)

<table>
<thead>
<tr>
<th>Reason</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Study participation too burdensome (n=41)</td>
<td>52%</td>
</tr>
<tr>
<td>(2) Not or no longer interested in study participation (n=17)</td>
<td>22%</td>
</tr>
<tr>
<td>(3) Too much distance between patients' home and study centre (n=12)</td>
<td>15%</td>
</tr>
<tr>
<td>(4) Disliked the aspect of randomisation (n=3)</td>
<td>4%</td>
</tr>
<tr>
<td>(5) No reason given (n=6)</td>
<td>8%</td>
</tr>
</tbody>
</table>

**Organizational level**

Ethical rules and regulations in the Netherlands warrant that a member of the medical team (e.g. nurse or doctor) approaches suitable patients for potential trial participation when recruitment is performed within the hospital. Although the underlying ethical
principle is important, for non-pharmacological research this is often a challenge because researchers involved in these studies (e.g. behavioural scientists) usually do not belong to the medical team and have to rely on the willingness of often-busy clinical nurses and oncologists to identify eligible patients. Consequently, in our study, this resulted in tension between the ethical requirement to rely on patient identification by clinical nurses and oncologists and the methodological necessity for approaching all patients who may be suitable. We tried to overcome this barrier by involving dedicated research nurses in patient recruitment for the study, as described above.

In addition, the primary eligibility criteria for our study were overly strict and study procedures were too complicated. For example, the study protocol required that screening for severe fatigue should be completed before the first cycle of treatment in the original study design. However, this was not feasible in clinical practice as other more urgent topics often needed to be discussed in the consultation prior to administration of the first cycle of treatment. To overcome these and other difficulties, we amended our eligibility criteria and study procedures during the study with approval of the funder of the study and the Medical Ethics Committee. Unfortunately, this was a lengthy process taking up to 12 months during which time we had to adhere to the original criteria and procedures. More procedures were adjusted and simplified such as inclusion of additional cancer types and more lines of anticancer therapy in order to widen the inclusion gate.

DISCUSSION

In the present paper, we evaluated patient recruitment for the Dutch TIRED study. During a period of 4 years, health care professionals from eight participating hospitals identified a total of 201 eligible patients of which the majority agreed to participate (n=122; 61% participation rate). Although this overall participation rate was satisfactory compared to other supportive care RCTs [14, 15], the total number of identified eligible patients was much lower than anticipated and it is likely that potential candidates have been missed.

Due to the slow recruitment for our trial, broadening of the original inclusion criteria, increase of participating centres and extension of our still ongoing recruitment period was necessary. This is in line with reports from other RCTs in patients with incurable cancer [3, 4]. Many investigators are struggling with challenges regarding the recruitment of study participants for RCTs and these issues are not limited to trials with incurable cancer patients. Briel et al. (2016) recently reported that one quarter of RCTs in general are discontinued with poor recruitment being the most frequently reported reason [16]. The most often mentioned reasons for recruitment failure were
overestimation of eligible patients and prejudiced views against effectiveness of trial interventions by recruiters and participants. We also encountered prejudiced views by doctors and nurses; mostly thinking study participation would be too burdensome for these seriously ill patients. In addition, defeatism about the prognosis and therefore not feeling that such supportive care studies could be of added value was also observed. Yet, in a previous study, we demonstrated that 93% of patients being treated for incurable cancer at least want to be informed about fatigue interventional studies and they did not differ in their preference from patients being treated with curative intent [17].

We experienced a substantial variation in the recruitment rate between study centres. Also, doctors and nurses indicated that screening potential candidates was often not possible because it required too much time. In part, this was caused by overly complex eligibility criteria and study procedures, demonstrating a need to more globally define eligibility criteria and better align study procedures with clinical practice. However, after amending these, limited time still remained a main barrier for doctors and nurses to identify patients. These findings seem to underline the importance of having dedicated local coordinators, such as research nurses, available on site in multicentre studies. Unfortunately, this was not foreseen in our study budget and thus we had insufficient funding available to hire dedicated research nurses at all sites.

The main reason for identified patients not accepting our study (39% of eligible patients) was that participation was perceived as too much of a burden. Indeed, the interventions offered in our study involved weekly hospital visits and associated travel arrangements over a period of 12 weeks coinciding with systemic cancer treatment. Several patients expressed concerns about burdening family members or friends for travel arrangements and preferred using their services for medical appointments. In some instances, we were able to offer taxi services or a financial compensation for friends or family members willing to shuttle patients to the hospital, which facilitated participation. For future trials, we recommend allocating resources for these types of services into study budgets. Alternatively, the emergence of e-Health and the development of self-management or home-based interventions offer the potential to reduce the intensity of the intervention as well as overcome the burden of distance for these patients.

We adopted a three-armed study design in line with our desire to test both the effects of CBT and GET compared to usual care. In hindsight, although three-armed studies are ambitious, we believe this might have been a bridge too far. Especially, taking into account that only a few two-armed RCTs focusing on supportive care interventions for CRF in a homogeneous sample of patients with incurable cancer have been conducted. However, the growing pressure and ongoing competition in obtaining
Lessons learned from the TIRED study

Research funding is associated with an incentive to propose ambitious and novel research. Moreover, in the Netherlands, funding for feasibility or pilot intervention studies in cancer research was very limited when we developed our study plans. Fortunately, in 2016, the Dutch Cancer Society launched a new way of funding in which they provide funding for so-called ‘unique high risk’ projects offering the possibility to perform short-term preparatory work to determine whether these early-stage ideas offer viable opportunities for further large-scale studies (https://www.kwf.nl/english/poi-english/). We believe that many of the barriers and challenges experienced in our study, would have been encountered in piloting the planned recruitment strategies.

Despite sharing valuable lessons learned from patient identification for our RCT in patients with incurable cancer, our findings have limitations that should be noted. We retrospectively calculated the number of patients that needed to be available for identification to eventually randomise the adapted sample size. In relation to the estimated total number of potentially eligible patients during the recruitment period, this number seemed feasible. However, we could only perform an indirect comparison, since specific information on the incidence of metastatic disease per participating hospital was not available. Ideally, investigators should obtain specific information regarding the number of patients that would meet their eligibility criteria for each hospital in the year prior to the start of intended patient recruitment. In addition, we shared lessons learned from a single Dutch study but the findings might not necessarily pertain to other countries with different rules, regulations and local situations, thus limiting the generalisability of our findings. Notwithstanding these differences, recruitment challenges are widespread and the findings from our study, particularly on the patient level and doctor and nurse level, may therefore also be important for researchers in other countries.

The present paper presented important lessons learned from the still ongoing Dutch TIRED study. In cancer research we are often focused too much on the output of RCTs and not enough on the processes by which the study was done. We learned that we need studies with less complicated procedures that are better aligned with routine clinical practice, with more globally formulated eligibility criteria, and examining less burdensome interventions delivered closer to or at the patients’ home, preferably. Also, we need more effective education preparing doctors and nurses involved in patient recruitment for these trials. Given their pivotal role in successful recruitment of participants, dedicated research nurses should be employed at each study centre. Accordingly, study budgets must include allocation of sufficient financial resources to adequately compensate research nurses for time spent on patient identification. Finally, we encourage other investigators to also share their valuable lessons learned.
REFERENCES


CHAPTER 10

SUMMARY AND GENERAL DISCUSSION
This thesis focused on cancer-related fatigue (CRF) with an emphasis on understudied cancer populations in psychosocial oncology, ranging from patients with a rare cancer diagnosis to patients with incurable disease. In this final chapter the previous chapters are summarised and discussed. Practical implications along with recommendations for future research are formulated.

SUMMARY

In Chapter 1 a general introduction on CRF research is provided. Despite the fact that CRF is a common symptom in patients with cancer, it is still underreported, underrecognized and undertreated. In particular, research on the prevalence, impact and management of severe fatigue in patients with a rare cancer diagnosis or incurable disease is scarce.

PART I: FATIGUE IN PATIENTS WITH RARE CANCER

Chapter 2 focused on the prevalence, impact, and correlates of severe fatigue in patients diagnosed with cancer during adolescence and young adulthood (AYA). Compared to older adults, a diagnosis of cancer between the ages of 18 and 35 years is rare. Severe fatigue based on a validated cut-off for severe fatigue occurred in 48% (n=40/83) of participating AYAs with cancer visiting a specialised AYA outpatient clinic. This proportion is significantly higher compared to the proportion of severely fatigued matched population-based controls, in which only 20% of 249 controls scored above the cut-off. We demonstrated that severely fatigued AYAs with cancer reported significantly lower quality of life on physical, psychological, social, and spiritual domains. Fatigue severity was associated with female gender, being unemployed (or not studying), late stage cancer at diagnosis, receiving active treatment at the time of study participation, palliative intent of treatment, and having had radiotherapy as part of cancer treatment. In addition, more fear of cancer recurrence and higher psychological distress were associated with higher CRF scores. The findings of this study emphasize the importance of careful attention for fatigue in AYAs with cancer. Screening for the presence of severe fatigue at regular intervals as well as the identification of treatable contributing factors (e.g. anemia, hypothyroidism, psychological distress, and sleep disorders) is warranted not only during cancer treatment but also after completion of treatment.
Chapter 3 described the results of a study on CRF conducted in patients with rare gastro-intestinal stromal tumors (GISTs). We used a validated cut-off for severe fatigue to assess the prevalence of CRF among a sample of 89 patients with GIST. The sample included patients with localized as well as metastatic disease. Sixty-one patients (69%) received treatment with tyrosine kinase inhibitors (TKIs) at the time of study participation. Severe fatigue occurred in 30% \(n=27/89\) of patients with GIST and in 33% \(n=20/61\) of patients with GIST on a TKI. The prevalence of severe fatigue was significantly higher in patients with GIST compared to the matched population-based controls. Severely fatigued patients with GIST reported poorer quality of life and were significantly more impaired on physical, role, emotional, cognitive, and social functioning compared to non-severely fatigued patients with GIST. The severity of fatigue was associated with the use of a TKI, more psychological distress, and lower self-reported physical functioning. Discontinuation of treatment with a TKI because of severe CRF is generally not an option, however, the other associated factors (i.e. psychological distress and lowered physical functioning) can be addressed by psychosocial and exercise interventions. Doctors could play a crucial role in informing severely fatigued patients about these psychosocial and behavioural factors that deserve appropriate management and may refer patients to existing evidence-based interventions for CRF that aim to address these factors.

We focused on CRF in patients with a rare diagnosis of chronic myeloid leukemia (CML) in Chapter 4. This once-fatal cancer has become a chronic disease leading to a normal life span in the majority of patients as a result of the introduction of TKIs. Yet, patients may need to take TKIs indefinitely and many of them suffer from TKI-related fatigue. Building upon an evidence-based intervention for fatigue in disease-free cancer survivors, i.e. cognitive behaviour therapy, we adapted this intervention to the specific needs of patients with CML receiving chronic TKI treatment. Guided by an adaptation framework, we used a series of systematic steps and adaptation methodologies, including semi-structured interviews with CML patients and health care providers, and feedback from topical experts. We aimed to gauge reactions to existing intervention content and a new delivery format. Furthermore, with the emergence of e-Health and to reduce travel burden, the adaptation also involved moving from a clinic-based face-to-face delivery to an Internet-assisted delivery format using video telephony and tablet computer technology (FaceTime using iPads). We found that patients were receptive to existing content topics and the Internet-assisted delivery format was acceptable. A key theme reflected the need for a new customized psycho-educational module about CML as a disease and its treatment. The results from this study have set the stage for the pilot RCT that is currently evaluating the usability, feasibility, and efficacy of the adapted CBT for TKI-related fatigue.
PART II: FATIGUE IN PATIENTS WITH INCURABLE DISEASE

Chapter 5 focused on dyadic agreement between patients with incurable cancer and their informal caregivers regarding patients’ fatigue severity during cancer treatment with palliative intent. In a longitudinal study, we examined to what extent patients and informal caregivers agreed on patients’ fatigue severity both on a continuous level as well as on the presence of severe fatigue based on a validated cut-off. A sample of 107 patients and their informal caregivers completed questionnaires at baseline and 69 dyads completed questionnaires six months later. At baseline, informal caregivers significantly overestimated patients’ fatigue severity with a moderate amount of bias. In 76% of the dyads there was agreement about the presence or absence of severe fatigue. On a group level, agreement did not change over time. However, on a dyad level, there was a tendency to either remain in agreement or reach agreement. In addition to baseline agreement, informal caregivers’ own fatigue severity and caregiver strain predicted their ratings of patients’ fatigue. For consultations where important treatment decisions are to be made, a second rating of patients’ fatigue by the informal caregiver may provide oncologists with a more complete reflection of patients’ fatigue and facilitate discussing how well patients are holding up with treatment. It is however important to take into account informal caregivers’ affective state when asking for judgements about patients’ fatigue, as their response is likely to be affected if the informal caregiver is fatigued or feeling strained.

Chapter 6 described the results of a Cochrane systematic review and meta-analysis, in which we included randomised controlled trials (RCTs) that investigated the effects of psychosocial interventions in patients with incurable cancer receiving systemic treatment with palliative intent and had fatigue as an outcome of interest. We included data from 12 studies (n=535) in the subset meta-analysis. Findings did not support the effectiveness of psychosocial interventions for reducing fatigue post-intervention. There were sources of potential bias, including a lack of description of methods of blinding and allocation concealment and small size of the study populations. We considered the overall quality of evidence to be very low. As such, the true effect is likely to be substantially different from the estimate of the effect. At present, there is a lack of evidence around the benefits of psychosocial interventions to reduce fatigue in patients with incurable cancer receiving cancer treatment with palliative intent. Additional studies with larger samples are required. In addition, studies should expand their focus beyond patients with metastatic breast cancer, as it is unknown whether findings from this most widely studied patient group generalize to patients with other cancer diagnoses. Multicentre studies investigating short interventions delivered over a period of several weeks or months, with follow-up assessment following shortly after intervention delivery are recommended.
As a result of the longer-term treatment of patients with incurable cancer, aspects regarding quality of life and symptom management become even more important. Fatigue is one of the most commonly reported symptoms during systemic cancer treatment for incurable cancer but there is a lack of evidence around the benefits of psychosocial and exercise interventions in this specific population. **Chapter 7** described the design and rationale for a multicentre three-armed RCT randomising patients with incurable cancer to either graded exercise therapy (GET), cognitive behaviour therapy (CBT) for severe fatigue or usual care (UC). GET and CBT for severe fatigue are delivered over 12 weeks in addition to UC. UC included treatment in concordance with national and regional cancer clinical practice guidelines. The primary outcome is fatigue severity. Secondary outcomes included functional impairments and quality of life. Outcomes will be assessed at baseline, post-intervention (14 weeks), and at follow-up 18 and 26 weeks post-randomisation. Outcomes at post-intervention of either treatment arm will be compared to those of UC participants. We aim to randomise a total of 219 severely fatigued patients from nine hospitals throughout the Netherlands.

Shortly after initiating the multicentre three-armed RCT described in Chapter 7, we experienced major difficulties in recruiting study participants. One of the main barriers to successful identification and enrolment of study participants for palliative or supportive care RCTs is professional gatekeeping. This gatekeeping is often related to the health care professionals’ perception that study participation might be too burdensome for the patient. In **Chapter 8** we examined whether professional gatekeeping of patients with incurable cancer from the aforementioned fatigue interventional study was justified from the patients’ perspective. In total, 229 patients completed a fatigue-screening questionnaire as part of routine care prior to the start of (a new line of) systemic treatment. In addition, patients were asked whether they agreed with being contacted by a researcher if their answers indicated the presence of severe CRF. In all, 93% (\(n=212\)) of patients agreed with being approached by a researcher to be informed about fatigue interventional studies. Of interest, agreement to be informed did not differ significantly between patients receiving treatment with curative (\(n=108\)) or palliative intent (\(n=106\)). In addition, 90% of those severely fatigued patients receiving systemic treatment with palliative intent agreed to being contacted by a researcher. Thus, the majority of patients who completed a fatigue-screening questionnaire also wanted to be informed by a researcher about available fatigue interventional studies, regardless of treatment intent. Our findings imply that there is no need for well-meant protection of patients receiving cancer treatment with palliative intent by withholding from them information about fatigue interventional studies.
Chapter 9 described lessons learned in patient identification and recruitment for the multicentre three-armed RCT described in Chapter 7. Although sufficient potential candidates were available for identification, we experienced a slow recruitment rate. Consequently, this resulted in the need to broaden our original inclusion criteria, extend the number of participating centres as well as the duration of the recruitment period. Barriers and challenges were faced at the doctor and nurse level, the patient level and the organisational level. Between January 2013 and December 2016, a total of 201 eligible patients were identified of which 122 were randomized. The inclusion rate varied largely between centers. The most frequently mentioned reason for non-participation of eligible patients was that study participation was perceived as ‘too burdensome’ (52%; \( n=41/79 \)). Ethical rules and regulations necessitate that a member of the medical team, such as a doctor or nurse, introduces the study to potential candidates before a researcher informs them. Yet, these health care professionals were often too busy to screen patients for eligibility and introduce the study. The overly strict primary eligibility criteria and complicated study procedures further impeded doctors and nurses in introducing the study to patients. Engagement of dedicated local coordinators, especially research nurses who have time allotted to identify potential candidates, was essential in successfully identifying patients.

GENERAL DISCUSSION

Fatigue in patients with a rare cancer diagnosis or incurable disease

The studies presented in this thesis focused on patients primarily characterized by a rare cancer diagnosis and patients diagnosed with incurable disease. These patient populations are largely understudied in psychosocial oncology. In addition, more and more patients from these groups are living longer with cancer as treatments have become more effective over time. For example, the introduction of targeted agents as a new class of cancer drugs have changed the therapeutic landscape for patients with CML and GIST in which they are used as the main systemic treatment nowadays. Targeted agents alongside immunotherapy are currently the focus of novel systemic treatment developments and form a cornerstone of personalised medicine. For an increasing number of patients, their disease may be controlled as long as patients are receiving cancer treatment but their cancer is not cured. Living with cancer is different from living after cancer. Next to prolonging patients’ lives, it is equally important to continue to live with the best possible quality of life. CRF is one of the symptoms that compromises patients’ quality of life and as such deserves more attention in both research and clinical practice.
Fatigue in patients with a rare cancer diagnosis versus patients with more common cancers

The first two studies presented in this thesis demonstrated that a considerable proportion of patients with a diagnosis of cancer at an uncommon age (AYA) and with a rare diagnosis of GIST experience severe fatigue during and after cancer treatment. In line with previous research in patients with more common cancers [1-5], the presence of severe fatigue significantly impaired all domains of patients’ quality of life. Because of the high prevalence and profound impact on quality of life, systematically screening of patients for the presence of severe fatigue at regular intervals is warranted. It should be the first step to increase awareness for fatigue by health care professionals and has been suggested before [6]. In agreement with previous studies on CRF in more common cancer populations [7-9], we found that several cognitive and behavioural factors were related to fatigue severity, such as psychological distress, fear of cancer recurrence, and lower self-reported physical functioning. Traditionally, CRF has often been attributed solely to the disease itself and its treatments. Yet, the studies in AYA cancer patients and GIST patients presented in this thesis demonstrated that these disease- and treatment-related factors are not the only factors associated with fatigue severity, which is also the case in patients with more common cancer types. In fact, strong correlations were found between psychological distress and self-reported physical functioning and fatigue severity in AYAs with cancer and patients with GIST. In contrast to disease- and treatment-related variables, these factors can actually be altered. A recent meta-analysis compared the four most commonly recommended interventions for CRF [10]. Exercise (i.e. aerobic, anaerobic, or both), psychological (i.e. cognitive behavioral or psycho-educational therapies), and exercise plus psychological interventions improved CRF during and after primary cancer treatment, whereas pharmacological interventions did not. The authors advised clinicians to prescribe exercise or psychological therapies as first-line interventions for CRF. AYA cancer patients and GIST patients suffering from severe fatigue might also benefit from these interventions that target behavioural and cognitive factors.

Targeted therapy-related fatigue

The transition from conventional chemotherapy to molecularly targeted cancer drugs has resulted in an increasing number of successful treatments that have impacted many cancer patients’ lives [11]. In addition to GIST and CML, TKIs are now also indicated in the treatment of many common cancers such as breast and lung cancer [12]. Despite the unprecedented clinical success of TKIs in the treatment of cancer, these targeted cancer drugs are associated with side effects that can impact patients’ quality of life [12]. As described in this thesis, CRF is a known side effect of TKI treatment in patients with GIST. In patients with CML on a TKI, chronic fatigue is the most important factor that limits patients’ quality of life [13]. However, the majority
of CRF research has been conducted in patients receiving more conventional cancer treatments such as chemotherapy, radiotherapy, and hormone therapy. With the increasingly common use of TKIs in the treatment of cancer, more knowledge on the prevalence, impact, course, and associated factors of TKI-related fatigue is needed. In addition, it remains to be examined whether existing evidence-based interventions addressing CRF that have been developed for and tested in patients receiving conventional treatments could also be applied in fatigued patients with extended TKI treatment.

Adapting existing evidence-based interventions for new target populations
Existing evidence-based interventions aimed at behavioural and cognitive factors that maintain fatigue have not been specifically examined in patients with a rare cancer diagnosis or incurable disease. One way to facilitate the translation of evidence-based interventions for CRF into clinical practice is to adapt existing interventions for application in new target populations. Our study in patients with CML treated with TKIs demonstrated that it is feasible to adapt an existing fatigue intervention to a new target population without changing the internal logic and core components of the intervention. Although results on efficacy from the ongoing pilot RCT are not yet available, the preliminary findings are promising (Jim et al., conference abstract submitted). This adaptation process could also be applied to other cancer populations in which fatigue interventions have not been examined extensively. For example, specific tailoring of the content and delivery of the intervention to the needs and age-specific situation of AYAs with cancer might increase efficacy of the intervention in this unique patient group. Finally, the adapted intervention for targeted therapy-related fatigue in CML might also be appropriate for patients being treated with TKIs for GIST, as these two patient groups are both receiving treatment with TKIs for an extended period.

Proxy rating of patients’ fatigue severity by informal caregivers
We found that informal caregivers, partners in most instances, are able to give a meaningful and accurate proxy rating of patients’ fatigue severity during cancer treatment with palliative intent. Accuracy was better for dichotomous ratings on the presence or absence of severe fatigue, than on a continuous level. The accuracy was influenced by caregivers own fatigue severity and strain. Previous research already demonstrated that almost a quarter of the informal caregivers suffered from severe fatigue and their mean fatigue severity score was higher compared to a healthy reference group [14]. Yet, proxy ratings of patients’ fatigue may add to the richness of available information that the doctor, patient and caregiver will need to collect when decisions on current and continuing further systemic treatment are to be made. This seems even more important with the availability of sequential novel cancer treatments.
and the need to often continue treatment for an extended period of time in order to control the disease for as long as possible. Because CRF affects not only the patient, but also the informal caregiver, careful consideration of the severity of CRF by including both the patient and the proxy rating seems a rational approach for clinical practice. However, it should be kept in mind that caregivers’ own fatigue severity and strain influence these ratings and thus doctors should also address these aspects in their consultation to put these ratings into perspective.

Difficulties in recruiting participants for fatigue interventional studies

Conducting fatigue interventional studies in patients with a rare cancer diagnosis or incurable disease is challenging. The most challenging aspect in both populations is recruitment of large enough samples. However, the reasons for the difficulties in patient recruitment differ. In patients with a rare cancer diagnosis, only a limited number of patients per year are being diagnosed with the condition even though the total incidence accounts for 24% of the total cancer prevalence in Europe [15]. For studies in these patients, it is critically important to collaborate with multiple institutions and establish (inter)national networks that participate in testing interventions in trials or to develop alternative designs for clinical experiments in these patients. For patients with a diagnosis of incurable cancer it is not the rarity of the disease but other aspects such as the seriousness of the condition or professional gatekeeping and attitudes of defeatism that impact the possibility to recruit sufficient sample sizes. In the Cochrane systematic review presented in this thesis, 14 RCTs were identified in which at least part of the patients were diagnosed with incurable disease. The 12 studies able to provide data for the subset meta-analysis including only patients with incurable disease had a limited total of 535 participants of interest to the review. Unfortunately, recruitment of severely fatigued incurable cancer patients for the RCT of which the design and rationale were presented in this thesis also proved to be challenging. Despite continued efforts of involved study personnel and the frequent discussions within the multidisciplinary study team, in which we tried to overcome barriers and challenges for patient identification, we did not reach our sample size within the envisioned and already extended recruitment period. The disappointing recruitment rate required a substantial extension of the recruitment period as well as inclusion of many more study centers and broadening of our original eligibility criteria on cancer types and treatment lines. We learned that future studies should be better aligned with routine clinical practice, have more globally formulated eligibility criteria, and should examine less burdensome interventions, delivered closer to the patients’ home. In addition, study budgets should include sufficient financial resources to hire dedicated local coordinators at each study site in multicentre trials.
DIRECTIONS FOR FUTURE RESEARCH

The aim of this thesis was to address CRF in patients with rare cancer or incurable disease. A consistent theme throughout the studies was the difficulty with recruiting large enough samples to assess fatigue and test the efficacy of interventions for fatigue. In the following paragraphs, directions for future research have been formulated based on several observations that were made in conducting the research presented in this thesis.

Single-case intervention research
One possibility to overcome some of the challenges in patient recruitment might be the use of alternative study designs, such as replicated experimental single-case studies. A single-case experimental (SCE) study is a rigorous, scientific methodology used to define basic principles of behaviour [16]. Because they document experimental control, it is an approach, like the golden standard RCT, that may be used to establish evidence-based practices. The SCE design has specific advantages compared to the RCT as they are comparatively quick, inexpensive, and easy to perform. Most importantly, the power is derived from the number of observations performed within each individual and thus this design is particularly useful for studying small-n populations or populations in which a full-scale traditional RCT is not feasible. We piloted this SCE methodology to examine the efficacy of our adapted CBT intervention for targeted therapy-related fatigue in five CML patients receiving treatment at the Radboud university medical center. The results of this study are expected at the end of 2017, but preliminary findings demonstrated the feasibility and acceptability of this design [17].

Improved assessment of CRF during cancer treatment
At present, enrolment of participants for RCTs often relies on identification of potential candidates by often-busy health care professionals. The study protocol for our RCT required that patients should be screened for the presence of severe fatigue prior to or during systemic cancer treatment with palliative intent. Due to ethical rules and regulations, a member of the patients’ medical team had to perform this fatigue screening. However, screening for severe fatigue by the nurse or doctor is not often a priority when several other medical topics need to be discussed during consultations. Including routine assessment of CRF during the course of cancer treatment using patient-reported outcomes (PROs) may be a viable strategy to enhance fatigue screening. To save time during consultations, patients could complete brief and electronic fatigue screening questionnaires prior to clinic visits and their data are automatically scored and available in reports to be viewed when the clinician meets the patient [18, 19]. Bennett et al. (2012) described the use and advantages of electronic PRO systems in oncology clinical practice [20]. The authors describe that the rapid
expansion and use of mobile devices facilitates the clinical use of electronic PRO systems. Data can be automatically transferred in real time to a computer server and data entry or calculation of a total score by staff is not required. Adding results to the patient’s electronic medical record allows for generation of alerts to notify clinicians when patients score above a clinical relevant threshold for fatigue. In addition, it enables clinicians to review patients’ CRF over time. The electronic system could then alert clinicians to current trials or existing evidence-based interventions when CRF persists over time within a patient. It would be interesting to examine whether these methods also facilitate improved patient identification and recruitment for fatigue interventional studies.

Patient involvement in intervention research
Another way to facilitate patient recruitment would be to collaborate more intensively with patients and patient organisations in intervention research. In addition to the limited time available in consultations, another well-known barrier to successful patient recruitment is professional gatekeeping resulting predominantly from the professionals’ perception that study participation might be too burdensome [21]. While this might be true for some patients, this cannot be generalized to the entire population. In fact, in one of the studies presented in this thesis we clearly demonstrated that gatekeeping is not justified from the patients’ perspective, with 93% of patients receiving cancer treatment with palliative intent agreeing to at least be informed about fatigue interventional studies. Unfortunately, we also experienced gatekeeping in the TIRED study. In addition, attitudes of defeatism were observed within clinicians, such as undermining that CRF is a symptom that can be effectively treated also in patients with incurable cancer. Indeed, the optimal approach for addressing CRF in patients receiving cancer treatment with palliative intent is yet to be determined, but there is substantial evidence from patients during and after adjuvant treatment for more common cancers [10, 22, 23] that CRF can be effectively treated. In light of the new era of patient-centred health care, it seems only reasonable to enable patients to also take a more active role in making their own decisions on participating in supportive care research. Consequently, participants for the previously described experimental SCE study in patients with CML were not only recruited by haematologists but also directly via an online platform for patients and health care professionals (http://www.cmylife.nl). Furthermore, a recently completed trial on the efficacy of a web-based version of CBT for severe fatigue in disease-free breast cancer survivors included both clinician-referred as well as self-referred patients. Self-referrals were successfully recruited via announcements on social media (i.e. Facebook and Twitter), on websites of the participating hospitals, and in local newspapers. In total, 42% (n=56/132) of the entire study sample consisted of self-referred patients (Abrahams et al., submitted for publication). We believe that efforts to promote patient-centredness should not be restricted to clinical care. Instead, intervention research should also be respectful of
and responsive to patient preferences, needs, and values. Therefore, it is suggested to place individual patients at the centre of what we do by informing all patients about available supportive care trials, e.g. by using social media, brochures in waiting rooms, websites, and newspapers. If patients are interested they can decide to discuss study participation with their health care provider instead of the other way round. This may also overcome the possibility of selection bias resulting from professional gatekeeping or attitudes of defeatism in health care providers.

**Home-based, e-Health, and technology-enhanced interventions**

Although the overall participation rate of identified and eligible patients (61%; \(n=122/201\)) was satisfactory, one of the main reasons for refusal of participation in the TIRED study was that participation was perceived as too burdensome. The two interventions under examination were delivered at or near the hospital where the patient was undergoing cancer treatment and involved weekly sessions in a period of 12 weeks. For future trials, we recommend researchers to consider transitioning from traditional clinic-based intervention delivery to home-based delivery using e-Health technologies. The World Health Organization defined e-Health as “the transfer of health resources and health care by electronic means” [24]. There are specific advantages to the use of Internet-based interventions in addressing CRF in patients with incurable cancer. First and foremost, it allows patients to receive the intervention at their own environment reducing travel burden and creating more efficient and convenient delivery of the intervention. As a result, health care professionals might also be more likely to refer patients for participation in these studies because the burden of participation is limited. Potential disadvantages of home-based Internet-assisted delivery also need to be acknowledged, such as getting participants to use the technologies at a high enough frequency over a specified duration to receive the desired dose of the intervention. Evidently, before transitioning to home-based or e-Health interventions, the first step for researchers would be to gauge how this patient population feels about these new ways of intervention delivery and what expectations and wishes they have. In addition to the Internet-assisted delivery channel of the intervention, one might also consider incorporating more technology in fatigue interventions itself. For example, as part of CBT for fatigue, cancer patients will often be advised to go to bed and wake at the same time each day to reduce bed and wake time variability and reset the biological clock. Smart phone technology may assist patients by alerting them 15 minutes prior to the scheduled bedtime and set automated alarms in the morning. Furthermore, wearable technologies such as smart watches or activity trackers provide both monitoring and real-time feedback applications and may facilitate the implementation of home-based exercise interventions. In addition, the use of automated responses in cognitive behavioral and exercise interventions might be a practical solution to reduce the amount of therapist time needed to deliver the intervention. For example, feedback on the sleep-wake
pattern or the distribution of activities in CBT for fatigue could be delivered by using automated responses based on predefined algorithms.

**CONCLUDING REMARKS**

To conclude, this thesis added to a better understanding of the prevalence, impact, and associated factors of CRF in patients with a rare cancer diagnosis. Research on severe fatigue in this population is scarce but our studies suggested that, despite the somewhat higher prevalence of severe fatigue, the impact and associated factors do not differ from patients with more common cancer diagnoses. This implies that these patients might also benefit from existing (adapted) evidence-based interventions for CRF. In addition, patients with incurable cancer have been relatively understudied in the area of CRF intervention research. Conducting high quality intervention research in this population by using a ‘golden standard’ RCT is particularly challenging. There is currently a lack of evidence around the benefits of exercise and psychosocial interventions for CRF in these patients. In the near future, we will complete a multicentre three-armed RCT that has the potential to significantly add to our knowledge on how to best address CRF in the growing population of patients living with a diagnosis of incurable cancer that are increasingly receiving life-extending cancer treatment.
REFERENCES


SAMENVATTING

Dit proefschrift is gericht op aan kanker gerelateerde vermoeidheid met bijzondere aandacht voor populaties die weinig bestudeerd zijn binnen de psychosociale oncologie, namelijk patiënten met een zeldzame kanker diagnose en patiënten met ongeneeslijke kanker. Hierna worden de verschillende hoofdstukken van het proefschrift samengevat en praktische implicaties en aanbevelingen voor toekomstig onderzoek voorgesteld.

Hoofdstuk 1 geeft een algemene inleiding over onderzoek naar aan kanker gerelateerde vermoeidheid. Ondanks het feit dat vermoeidheid een veelvoorkomend symptoom is bij patiënten met kanker, wordt het nog steeds te weinig gerapporteerd door patiënten, wordt het onvoldoende herkend en onvoldoende behandeld. Met name het onderzoek naar de prevalentie, gevolgen en behandeling van ernstige vermoeidheid bij patiënten met een zeldzame of ongeneeslijke vorm van kanker is schaars.

DEEL I: VERMOEIDHEID BIJ PATIËNTEN MET EEN ZELDZAME VORM VAN KANKER

Hoofdstuk 2 richt zich op het vaststellen van de prevalentie van ernstige vermoeidheid bij patiënten waarbij kanker tijdens de adolescentie en jong volwassenheid (AYA) werd gediagnosticeerd. Tevens wordt onderzocht wat de impact is van ernstige vermoeidheid en welke factoren hieraan bijdragen. Een diagnose van kanker op de leeftijd van 18 tot 35 jaar is zeldzaam. Ernstige vermoeidheid op basis van een gevalideerde afkapwaarde kwam voor bij 48% (n=40/83) van de deelnemende AYA’s met kanker die een gespecialiseerde AYA polikliniek bezochten. Dit percentage is aanzienlijk hoger dan de prevalentie in de algemene populatie, waarin slechts 20% van de op leeftijd en geslacht gematchte groep ernstig vermoeid is. Ernstig vermoeide AYA’s met kanker hebben een aanzienlijk lagere kwaliteit van leven, zowel op fysieke, psychologische, sociale als spirituele domeinen. De ernst van de vermoeidheid was geassocieerd met geslacht (vrouw), werkloosheid (of niet studerend), een gevorderd stadium van kanker bij diagnose, actieve behandeling ten tijde van het invullen van de vragenlijst, palliatieve intentie van de behandeling en eerdere radiotherapie. Daarnaast waren ook angst voor terugkeer van de kanker en psychische distress geassocieerd met hogere vermoeidheidsscores. De bevindingen van deze studie benadrukken het belang van zorgvuldige aandacht voor vermoeidheid bij AYA’s met kanker. Op grond van de resultaten is het aan te bevelen om regelmatig te screenen op de aanwezigheid van ernstige vermoeidheid en om behandelbare factoren te identificeren (bijvoorbeeld psychische klachten en slaapstoornissen), niet alleen tijdens de behandeling, maar ook na afronding van de behandeling.
Samenvatting

Hoofdstuk 3 beschrijft de resultaten van een studie over aan kanker gerelateerde vermoeidheid bij patiënten met zeldzame gastro-intestinale stroma tumoren (GIST). We gebruikten een gevalideerde afkapwaarde voor ernstige vermoeidheid om de prevalentie van vermoeidheid in een steekproef van 89 patiënten met GIST te bepalen. De steekproef omvatte patiënten met zowel gelokaliseerde als gemetastaseerde ziekte die op de polikliniek medische oncologie en chirurgische oncologie behandeld werden. Eenenzestig patiënten (69%) werden op het moment van deelname aan het onderzoek behandeld met tyrosine kinase remmers (TKIs). Ernstige vermoeidheid kwam voor bij 30% ($n=27/89$) van de patiënten met GIST en bij 33% ($n=20/61$) van de patiënten met GIST die met een TKI behandeld werden. De prevalentie van ernstige vermoeidheid was significant hoger bij patiënten met GIST in vergelijking met de controlepersonen uit de algemene populatie, die gematched waren op geslacht en leeftijd. Ernstig vermoeide patiënten met GIST rapporteerden een lagere kwaliteit van leven en waren significant meer beperkt op het gebied van lichamelijk, emotioneel, cognitief en sociaal functioneren in vergelijking met niet vermoeide patiënten met GIST. De ernst van de vermoeidheid was geassocieerd met het gebruik van een TKI, meer psychische distress en verminderd lichamelijk functioneren. Het staken van de behandeling met een TKI vanwege ernstige vermoeidheid is in het algemeen geen optie, maar voor de andere geassocieerde factoren (psychische klachten en verlaagd fysiek functioneren) kunnen psychosociale interventies en interventies gericht op lichamelijke activiteit een nuttige aanpak zijn. Artsen kunnen een cruciale rol spelen door ernstig vermoeide patiënten te informeren over de bijdrage van psychosociale en gedragsmatige factoren aan de vermoeidheid en door hen te verwijzen naar hierop gerichte en bewezen effectieve interventies.

Hoofdstuk 4 richt zich op vermoeidheid bij patiënten met een andere zeldzame vorm van kanker, chronische myeloïde leukemie (CML). Deze tot het begin van dit millennium dodelijke vorm van kanker heeft zich als gevolg van de introductie van TKIs ontwikkeld tot een chronische ziekte met een levensverwachting die voor de meeste patiënten niet van de algemene populatie verschilt. Patiënten moeten de TKIs echter voor onbepaalde tijd gebruiken en velen van hen lijden aan TKI gerelateerde vermoeidheid. Wij hebben een bewezen effectieve interventie voor vermoeidheid bij patiënten genezen van kanker, namelijk cognitieve gedragstherapie (CGT), toegespitst op de specifieke behoeften van patiënten met CML die chronische behandeling met TKIs krijgen. De interventie werd geanalyseerd volgens een in de literatuur beschreven model. Door middel van semi-gestructureerde interviews met CML patiënten en zorgverleners werden de reacties op de bestaande inhoud en vorm van de interventie gepeild. In aanvulling op de inbreng van patiënten en zorgverleners werd ook feedback gevraagd aan deskundigen op het gebied van vermoeidheidsinterventies. Mede om de reisbelasting te verminderen, werd de overgang van een face-to-face interventie naar een interventie via het internet op basis van video-telefonie (Face-
time) via iPads voorgesteld. De resultaten lieten zien dat patiënten open stonden voor het gebruik van de op CML toegespitste interventie en positief waren over het volgen van de interventie via Internet. Het bleek nodig een nieuwe psycho-educatieve module over de ziekte CML en de behandeling ervan toe te voegen aan de bestaande inhoud. De resultaten van deze studie vormden de basis voor een onderzoek dat de bruikbaarheid, haalbaarheid en effectiviteit van deze toegespitste CGT voor TKI gerelateerde vermoeidheid bij CML onderzocht. Deze studie loopt momenteel in de Verenigde Staten.

DEEL II: VERMOEIDHEID BIJ PATIËNTEN MET ONGENEESLIJKE KANKER

In Hoofdstuk 5 hebben we gekeken naar de overeenstemming tussen patiënten met ongeneeslijke kanker en hun mantelzorgers met betrekking tot de ernst van de vermoeidheid van de patiënt tijdens de behandeling van kanker met palliatieve intentie. In een longitudinale studie hebben we onderzocht in hoeverre patiënten en mantelzorgers overeenstemming hadden over de ernst van de vermoeidheid van de patiënt. De ernst van de vermoeidheid werd gemeten met een totaalscore en op basis van een gevalideerde afkapwaarde. Honderdzeven patiënten en hun mantelzorgers vulden vragenlijsten in bij aanvang van het onderzoek, waarvan 69 koppels zes maanden later de vragenlijsten opnieuw invulden. Bij aanvang van het onderzoek overschaten mantelzorgers de ernst van de vermoeidheid van patiënten. Tegelijkertijd was er in 76% van de koppels overeenstemming over de aanwezigheid of afwezigheid van ernstige vermoeidheid. Op groepsniveau veranderde de overeenstemming niet in zes maanden. Echter, binnen koppels was er een tendens om ofwel het eens te zijn ofwel het eens te worden over de ernst van de vermoeidheid van de patiënt. Naast de overeenstemming bij aanvang, waren de ernst van de eigen vermoeidheid en de belasting van de mantelzorger voorspellers van hun beoordeling van de ernst van de vermoeidheid van patiënten. Tijdens consulten waarin belangrijke beslissingen over de medische behandeling moeten worden genomen kan een beoordeling van de vermoeidheid van patiënten door mantelzorgers, oncologen voorzien van een vollediger beeld van de vermoeidheid van de patiënt. Dit kan tevens het gesprek faciliteren over hoe goed patiënten de medische behandeling verdragen. Het is echter van belang om rekening te houden met de vermoeidheid en belasting van de mantelzorger wanneer zij uitspraken doen over de ernst van de vermoeidheid van de patiënt, aangezien de reactie van de mantelzorgers gekleurd kan zijn door de eigen mate van vermoeidheid.

Hoofdstuk 6 beschrijft de resultaten van een Cochrane systematische review en meta-analyse van gerandomiseerde en gecontroleerde studies die het effect van psychosociale interventies op vermoeidheid bij patiënten met ongeneeslijke kanker
tijdens systemische behandeling met palliatieve intentie hebben onderzocht. In de subgroep meta-analyse konden we gegevens opnemen uit 12 studies \((n=535)\). De bevindingen bieden geen ondersteuning voor de effectiviteit van psychosociale interventies voor het verminderen van vermoeidheid direct na de interventie. Er waren bronnen van potentiële bias, waaronder een gebrek aan beschrijving van de methoden van blindering bij toewijzing van een interventie aan deelnemers en blindering ná toewijzing, alsmede de kleine omvang van de steekproef. De algehele kwaliteit van het bewijs wordt als zeer laag beschouwd. Hierdoor verschilt het werkelijke effect waarschijnlijk aanzienlijk van de schatting van het effect. Op dit moment is er onvoldoende bewijs dat psychosociale interventies de vermoeidheid van patiënten met ongeneeslijke kanker, die behandeld worden met palliatieve intentie, kunnen doen verminderen. Aanvullende studies met een grotere steekproef zijn nodig. Bovendien dienen studies hun focus te verbreden door zich niet alleen te richten op patiënten met uitgezaaide borstkanker, aangezien niet bekend is of de bevindingen uit deze meest bestudeerde patiëntengroep ook gelden voor patiënten met andere kankerdiagnoses. Op grond van het voorgaande wordt aanbevolen om multicenter studies te initiëren die korte interventies over een periode van enkele weken of maanden onderzoeken en die een follow-up evaluatie hebben kort na afloop van de interventie.

Als gevolg van de steeds langduriger behandeling van patiënten met ongeneeslijke kanker zijn aspecten van kwaliteit van leven en symptoombestrijding nog belangrijker geworden. Vermoeidheid is een van de meest voorkomende symptomen tijdens de systemische behandeling van ongeneeslijke kanker, maar er is onvoldoende bewijs dat psychosociale interventies en interventies gericht op fysieke activiteit voor vermoeidheid in deze specifieke populatie effectief zijn. **Hoofdstuk 7** beschrijft de opzet en rationale voor een multicenter driearmige, gerandomiseerde en gecontroleerde interventiestudie bij patiënten met ongeneeslijke kanker waarin het effect van graded exercise therapie (GET; therapie gericht op een verbetering van de lichamelijk conditie door stapsgewijze toename van lichamelijke activiteit) of cognitieve gedragstherapie (CGT; therapie gericht op het veranderen van gedachten en gedrag die de vermoeidheid in stand houden) vergeleken wordt met gebruikelijke zorg. GET en CGT worden gegeven gedurende 12 weken in aanvulling op gebruikelijke zorg. Gebruikelijke zorg omvat behandeling in overeenstemming met de nationale en regionale oncologische richtlijnen voor de klinische praktijk. De primaire uitkomstmaat in de studie is ernst van de vermoeidheid. Secundaire uitkomstmaten zijn functionele beperkingen en kwaliteit van leven. De effecten van beide interventies zullen worden gemeten op baseline, direct na de interventie (14 weken) en bij follow-up 18 en 26 weken na randomisatie. De uitkomsten direct na de interventie worden voor iedere interventie apart vergeleken met de uitkomsten van de deelnemers die alleen gebruikelijke zorg hebben gekregen. We streven naar het randomiseren van in totaal 219 ernstig vermoeide patiënten uit negen ziekenhuizen.
Kort na de start van het interventieonderzoek beschreven in hoofdstuk 7 ondervonden wij problemen met het werven van deelnemers voor de studie. Eén van de belangrijkste belemmeringen voor succesvolle identificatie en inclusie van deelnemers voor studies gericht op palliatieve of ondersteunende zorg is professionele gatekeeping. Deze gatekeeping is vaak gerelateerd aan de perceptie van de zorgprofessional dat deelname aan de studie te belastend voor de patiënt is. In Hoofdstuk 8 hebben we onderzocht of professionele gatekeeping van patiënten met ongeneeslijke kanker voor een interventiestudie gericht op ernstige vermoeidheid gerechtvaardigd was vanuit het perspectief van de patiënt. In totaal hebben 229 patiënten in het kader van reguliere zorg een screeningsvragenlijst voor vermoeidheid ingevuld voor aanvang van (een nieuwe lijn) systemische behandeling. Daarnaast werd patiënten gevraagd of zij akkoord gingen met benadering door een onderzoeker indien er sprake was van ernstige vermoeidheid. In totaal stemde 93% (n=212) van de patiënten in met benadering door een onderzoeker om geïnformeerd te worden over de interventiestudie gericht op ernstige vermoeidheid. Er werd geen verschil gezien tussen patiënten die behandeld werden met curatieve (n=108) of palliatieve intentie (n=106), ten aanzien van hun instemming om geïnformeerd te worden (91% versus 93%). Bovendien stemde 90% van de ernstig vermoeide patiënten die systemische behandeling met palliatieve intentie kregen in met benadering door een onderzoeker. De meerderheid van de patiënten die een screeningsvragenlijst voor vermoeidheid invulde, wilde dus ook geïnformeerd worden door een onderzoeker over beschikbare interventiestudies voor ernstige vermoeidheid, ongeacht de intentie van de behandeling. Onze bevindingen impliceren dat er geen noodzaak is voor goed bedoelde bescherming van patiënten die behandeling met palliatieve intentie krijgen door hen informatie over interventiestudies voor vermoeidheid te onthouden.

Hoofdstuk 9 beschrijft de lessen die geleerd zijn ten aanzien van de identificatie en werving van patiënten voor het interventieonderzoek beschreven in hoofdstuk 7. Hoewel voldoende potentiële kandidaten beschikbaar waren, was de inclusie lager dan verwacht. Als gevolg hiervan was het noodzakelijk om onze oorspronkelijke inclusiecriteria aan te passen, het aantal deelnemende centra uit te breiden en de duur van de wervingsperiode te verlengen. Er waren belemmerende factoren voor de werving bij de arts en verpleegkundige, op het niveau van de patiënt en de ziekenhuisorganisatie. Tussen januari 2013 en december 2016 werden in totaal 201 patiënten geïdentificeerd die in aanmerking zouden kunnen komen voor deelname aan de studie waarvan er uiteindelijk 122 werden gerandomiseerd. De inclusiesnelheid varieerde sterk tussen de centra. De meest genoemde reden voor het weigeren van deelname door patiënten was dat studiedeelname door hen als te belastend werd beschouwd (52%; n=41/79). Ethische regels en voorschriften vereisen dat een lid van het behandelteam, zoals een arts of verpleegkundige, de studie bij een potentiële kandidaat introduceert voordat de onderzoeker hen informeert. Deze zorgprofessionals
zijn echter vaak te druk om patiënten te screenen op geschiktheid en de studie te introduceren. De zeer strikte oorspronkelijke inclusiecriteria en studieprocedures belemmerden artsen en verpleegkundigen verder in het introduceren van de studie aan patiënten. Het betrekken van toegewijde lokale coördinatoren, in het bijzonder researchverpleegkundigen die tijd hebben om potentiële kandidaten te identificeren, blijkt van essentieel belang in het succesvol identificeren van patiënten.

In Hoofdstuk 10 worden de praktische implicaties van de bevindingen beschreven en aanbevelingen voor toekomstig onderzoek voorgesteld. Het proefschrift heeft geleid tot een beter begrip over de prevalentie van aan kanker gerelateerde vermoeidheid bij patiënten met een zeldzame kanker diagnose. Daarnaast heeft het inzicht gegeven in wat de impact is van ernstige vermoeidheid en welke factoren hieraan bijdragen. Onderzoek naar ernstige vermoeidheid in deze populatie is schaars. De studies die zijn beschreven in dit proefschrift laten zien dat ondanks de ietwat hogere prevalentie van ernstige vermoeidheid bij patiënten met een zeldzame kanker diagnose, de impact en de factoren die hieraan bijdragen niet verschillen ten opzichte van patiënten met meer voorkomende kanker diagnoses. Hieruit volgt dat patiënten met zeldzame kanker diagnoses mogelijk ook kunnen profiteren van bestaande (aangepaste) bewezen effectieve interventies voor aan kanker gerelateerde vermoeidheid. Vermoeidheid bij patiënten met een ongeneeselijke vorm van kanker wordt eveneens relatief weinig bestudeerd. Dit geldt in het bijzonder voor interventieonderzoek naar aan kanker gerelateerde vermoeidheid. Het uitvoeren van gerandomiseerde en gecontroleerde studies, de ‘gouden standaard’ voor interventieonderzoek, is niet eenvoudig. Er is op dit moment onvoldoende bewijs dat met interventies gericht op fysieke activiteit of met psychosociale interventies de vermoeidheid van deze patiënten verminderd kan worden. In de nabije toekomst zullen wij een uniek en grootschalig interventieonderzoek afronden dat in belangrijke mate zal bijdragen aan de kennis over hoe aan kanker gerelateerde vermoeidheid het best aangepakt kan worden in de steeds groter wordende populatie van patiënten die leven met een diagnose van ongeneeslijke kanker en daarvoor steeds meer en langduriger behandeld worden.
LIST OF PUBLICATIONS

Peer-reviewed articles


Manuscripts

238


### Published abstracts


# PHD PORTFOLIO

**Name PhD student:** Hanneke Poort  
**Department:** Medical Psychology  
**Graduate School:** Radboud Institute for Health Sciences  
**PhD period:** 01/09/2012 – 01/07/2017  
**Promotor(s):** Winette van der Graaf, Gijs Bleijenberg, Hans Knoop  
**Co-promotor(s):** Stans Verhagen

## TRAINING ACTIVITIES

<table>
<thead>
<tr>
<th>a) Courses &amp; Workshops</th>
<th>Year(s)</th>
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<tbody>
<tr>
<td>- NCEBP (RIHS) introductie cursus</td>
<td>2013</td>
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<tr>
<td>- Good Clinical Practice (GCP) / BROK cursus</td>
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<td>- Presentation Skills</td>
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<td>- Onderzoeksdag Medische Psychologie</td>
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<td>- RIHS course ‘How to write a medical scientific paper’</td>
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<td>- Radboud Da Vinci Challenge</td>
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| b) Seminars & lectures | N/A | N/A |

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<th>c) Symposia &amp; congresses</th>
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<tr>
<td>- NVPO congress, Utrecht (poster)</td>
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<td>- Member NVPO congress committee</td>
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## TEACHING ACTIVITIES

| e) Lecturing | N/A | N/A |

| f) Supervision of internships / other | N/A | N/A |

**TOTAL** 49.5
Het einde kroont het werk. Dank ben ik verschuldigd aan iedereen die heeft bijgedragen aan het eindresultaat, mij op weg heeft geholpen, een klein of een groter stuk op mijn promotiepad heeft meegelopen en mij onderweg heeft aangemoedigd of gesteund. De onderstaande personen wil ik graag in het bijzonder danken.

Alle patiënten die deel hebben genomen aan de verschillende studies beschreven in dit proefschrift ben ik grote dank verschuldigd. Ik heb veel geleerd van hetgeen jullie met ons hebben willen delen en ben dankbaar voor jullie openhartigheid. Jullie motiveren me om door te gaan met het werk dat ik zo graag doe.

De leden van mijn promotieteam: Hans Knoop, jij was diegene die mij het vertrouwen en de kans gaf de TIRED studie op te zetten en uit te voeren, waar ik je -ondanks het vele vallen en opstaan- erg dankbaar voor ben. Je hebt me opgeleid tot een kritisch onderzoeker en gaf altijd duidelijke sturing. Ik ben blij dat niet alleen plan B, maar ook plan A tot een goed einde zal komen. Winette van der Graaf, jij hebt vele kansen gecreëerd en ze mij gegund. Dank voor je deskundige en positief kritische inbreng in de totstandkoming van dit proefschrift. Jouw hartstocht voor het verbeteren van niet alleen medisch oncologische, maar ook psychosociale zorg is uniek en bewonderenswaardig. Gijs Bleijenberg, als grondlegger van de onderzoekslijn vermoeidheid bij kanker ben ik je dankbaar voor de kennis en kunde die je aan de nieuwe generatie onderzoekers hebt willen overdragen. Hoewel je kort voor ik begon met emeritaat ging, bleef je op afstand betrokken bij mijn onderzoek. Stans Verhagen, jij wilde van mij niet alleen een hele doctor maken, maar ook een halve dokter. Ik heb met plezier en enthousiasme van je geleerd over de medische oncologie en palliatieve zorg. Bovendien wist jij als supportive care specialist en copromotor op precies de juiste momenten steun en aanmoediging te geven, waarvoor mijn dank.

Prof. dr. van Leeuwen, prof. dr. Witjes en prof. dr. van der Rijt dank ik voor het kritisch lezen en beoordelen van het manuscript en uw deelname aan de oppositie.

Co-auteurs, dank voor jullie waardevolle feedback en bijdrage aan de verschillende hoofdstukken. De multidisciplinaire samenwerking met bevolgen collega’s is één van de redenen waarom ik onderzoek doen zo leuk vind. Marlies, makkelijker konden we de uitvoer van de TIRED studie en de Cochrane review niet maken, maar in samenwerking met jou was het absoluut leuker! Je luisterend oor en relativeringsvermogen heb ik zeer gewaardeerd. Marieke, jouw toegankelijke begeleiding bij het schrijven van de eerste manuscripten zorgde voor een fijne start. Dank ook voor het met interesse volgen van mijn andere projecten. Olga, dank voor de introductie in het bijzondere onderzoek bij AYA’s met kanker en de leuke tijd in Edinburgh, London en Nederland.
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Dear Dr. Tulsky, thank you very much for the opportunity to start working with you and the entire Faculty at the Department of Psychosocial Oncology and Palliative Care at Dana-Farber and Harvard Medical School. I am extremely pleased to be one of the fellows and look forward to many great learning experiences the next two years.


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**Vriendinnen en vrienden** verdienen een speciaal plekje in dit dankwoord. Dank voor jullie nooit aflatende belangstelling in al die jaren voor niet alleen mijn onderzoek, maar juist ook voor al het andere. Ik heb genoten van de ontspanning en afleiding wanneer ik met jullie was en van het samen delen of vieren van grote en kleine gebeurtenissen in ieders leven. Zonder jullie had ik het niet kunnen volhouden. Hoewel ik mijn vertrouwde plek voor een tijdje ga verlaten, houd ik me vast aan wat één van jullie laatst wijselijk zei: “Je laat niets achter, je krijgt er alleen iets bij”.

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Lieve Bart en Mirte, mijn grote broer en schone zus, er was vanuit jullie nooit een tekort aan steun, afleiding en aanmoediging, waarvoor mijn grote dank. De gezamenlijke weekenden in Brabant, Texel of Italië deden mij altijd goed en ik kijk er nu al naar uit jullie in Boston te ontvangen. We vinden elkaar in een passie voor het goede leven, zijn echte familiemensen en hebben aan ambitie geen gebrek. Ik ben ontzettend trots op alles wat jullie zo ‘meesterlijk’ hebben bereikt. Liefste Femke en Siem, jullie zorgden er met jullie vrolijke energie vaak genoeg voor dat ik even vergat dat ik een proefschrift moest afronden. Ik ben een apetrotse tanti.

CURRICULUM VITAE


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