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# Internet-based cognitive behavioral therapy for breast cancer survivors with treatment-induced menopausal symptoms

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# CONTENT

CHAPTER 1

# GENERAL INTRODUCTION

## BREAST CANCER: TREATMENT AND SIDE-EFFECTS

The incidence and survival rates for breast cancer (BC) are rising, resulting in a rapidly growing group of BC survivors. In the Netherlands, 1 out of 7 women develop breast cancer, and in 2018 there were approximately 135,000 BC survivors [1, 2]. The rising incidence rates mainly reflect the better and earlier screening and detection of cancer, as well as the growing elderly population. The increasingly more sophisticated and effective arsenal of medical treatments also has contributed to the higher survival rates. Currently, the 5-year survival rates for invasive BC are as high as 90% [1, 2].

The treatment of breast cancer is not without side-effects. The side-effects can broadly be classified according to time of origin (i.e. short-term or late onset), and their nature (i.e. physical or psychosocial symptoms). In the short-term, patients experience side-effects like nausea, hair loss, fatigue and peripheral sensory neuropathy. Other side-effects, which typically develop at a later stage, include lymphedema, fear of disease recurrence, depression, and sexuality and intimacy problems. Some of these side-effects, like fatigue, can also become chronic in nature [2-6]. Younger women are at higher risk of developing psychosocial problems than older patients [7, 8], and they often report specific, age-related problems and needs. An obvious example is fertility problems caused by the BC treatment [9, 10]. Adjuvant chemotherapy, endocrine treatment and an oophorectomy, all commonly administered treatments for BC, affect the reproductive system by either damaging the ovaries, suppressing the uptake of reproductive hormones, or by complete removal of the ovaries. In turn, this can result in debilitating, treatment-induced menopausal symptoms [3, 11-13].

Menopausal symptoms include hot flushes and night sweats (HF/NS), vaginal dryness, decreased libido, dysuria, urinary incontinence, insomnia, dyspareunia, weight gain and psychological distress. Of these symptoms, HF/NS are the most prevalent and disruptive [14-20]. They also negatively impact health-related quality of life (HRQOL) [12, 15, 16, 21, 22] and can lead women to discontinue their endocrine treatment [23, 24]. The mean duration of HF/NS in BC survivors is nearly 6 years [25]. BC survivors experiencing these symptoms report unmet needs and interest in receiving treatment for them [14, 26-28].

## ETIOLOGY AND EXPERIENCE OF HOT FLUSHES AND NIGHT SWEATS

A disrupted thermoregulatory system plays a key role in the etiology of HF/NS. During the menopausal transition, the so-called thermoneutral zone is narrowed (see Figure 1), and thus fluctuations in body temperature more easily results in the experience of HF/NS [29-31].

The decline in estrogen, and not the absolute plasma levels, affects this system. However, decline in estrogen levels is a necessary but not sufficient cause of HF/NS. Dysfunctions in the hypothalamus and changes in the secretion of serotonin, norepinephrine and neurokinin B all impact the thermoregulatory homeostasis [29-32]. The exact role of and interplay between these changes is still not fully understood.

As the decline in estrogen levels among women experiencing treatment-induced menopause is acute and steep, it has been hypothesized that these women experience more frequent and more severe HF/NS than women experiencing naturally occurring menopause. This hypothesis has been confirmed by studies comparing the prevalence and severity of menopausal symptoms in women who underwent risk-reducing prophylactic salpingo-oophorectomy with women experiencing naturally occurring symptoms [33, 34]. However, to the best of our knowledge, such studies have not yet been conducted comparing BC survivors with treatment-induced menopausal symptoms and healthy women who have undergone menopause.

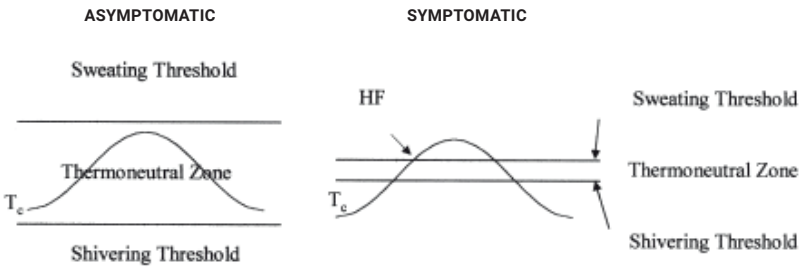


**Figure 1.** Thermoneutral zone in premenopausal (asymptomatic) and postmenopausal (symptomatic) women (adapted and reprinted with permission from Freedman [29]). Abbreviations: HF, hot flush; Tc, small core body temperature elevations.

There are several ways to measure the different features of HF/NS. Monitoring sternal skin conductance is used to objectively establish the frequency of HF/NS, while self-report questionnaires address frequency, severity and perceived impact of HF/NS, and thus provide more insight into the subjective experience of these symptoms [35-38]. The concordance rates between objective and subjective measures of the frequency of HF/NS are not high (range = 29% to 56%) [35, 36, 39]. Although so-called recall bias might explain some of the differences in objective versus subjective measures of HF/NS, other psychological processes may be equally if not more important. For example, selective attention to bodily sensations could lead women to over-report the frequency of HF/NS, while attributing a physiologically confirmed HF/NS to something else will lead to underreporting [36]. It is important to note that the experienced symptom burden, instead of the frequency of HF/NS, is the strongest predictor of help-seeking behavior in women experiencing menopausal symptoms [38].

## TREATMENT FOR MENOPAUSAL SYMPTOMS

### Pharmacological treatment options

There are several medical treatment options available for menopausal symptoms [40-42]. The most effective pharmacological treatment is hormone replacement therapy (HRT). However, HRT is contraindicated in BC survivors, since it is associated with an increased risk of BC and it can interfere with the endocrine treatment prescribed for women with hormone-sensitive BC [43]. Other, non-hormonal treatments include antidepressants, especially serotonin selective reuptake inhibitors (SSRI's), clonidine and gabapentin. Although these are moderately effective treatments, they are also associated with bothersome side-effects including insomnia, hypotension, dizziness, and suppressed libido [44-47]. More recently, promising results (i.e. decreased frequency of and bother by HF/NS) have been reported of neurokinin 3 receptor antagonists in phase II trials (which focus on drug safety and efficacy) [32, 48, 49]. Larger phase III trials evaluating the efficacy and related side-effects of this treatment are needed.

## Non-pharmacological treatment options

In a study by Hunter and colleagues [14], BC survivors reported a preference for non-pharmacological treatment for their HF/NS. These non-pharmacological treatments can consist of psychosocial approaches and complementary and alternative medicine (CAM) like acupuncture, yoga, hypnosis and herbal medicine. Only behavioral interventions (e.g. focusing on relaxation, paced breathing or physical exercise) and especially cognitive behavioral therapy (CBT) have a sound evidence-base obtained from multiple randomized controlled trials (i.e. level I evidence) [50-53]. For this reason, CBT is recommended as a treatment for HF/NS by the North American Menopause Society [54].

## Cognitive behavioral therapy

Hunter and colleagues [38] developed a cognitive behavioral model of HF/NS in which they underscore the interplay between, and impact of a) information input (internal and external triggers of HF/NS), b) symptom perception, c) cognitive appraisal and d) behavioral reactions. These elements form the foundation of their CBT program [55]. This CBT program is primarily aimed at helping women cope with their HF/NS, but also involves stress reduction, as high stress levels can potentiate HF/NS [31, 56]. Other commonly experienced menopausal symptoms such as sleep problems are also addressed by the program.

The CBT intervention consists of psycho-education, and women are actively encouraged, via homework assignments, to monitor and modify precipitants of HF/NS, practice relaxation techniques (e.g. paced breathing) and monitor and modify cognitions and behaviors related to HF/NS [57]. Each of these components is designed to target one or more of HF/NS premises, presented in Table 1: information input, symptom perception, cognitive appraisal and behavioral reactions. For example, by encouraging participants to practice stress reduction techniques like paced breathing, stress levels can be decreased which in turn can lead to an increased width of the thermoneutral zone. Furthermore, stress reduction techniques can also be used as an effective coping strategy for HF/NS [37, 38, 57].

Prior to the start of the current study, three randomized controlled trials (RCTs) had demonstrated the efficacy of this CBT program in reducing menopausal symptom burden in healthy women and in BC survivors with menopausal symptoms [58-60]. Ayers and colleagues [60] included 140 women from the general population in the MENOS 2 trial, to evaluate the

efficacy of group-based and minimally guided self-help CBT compared to a control group in reducing the perceived impact of HF/NS. Short- and longer-term results indicated significantly greater reductions in perceived impact of HF/NS for both CBT formats, i.e. group-sessions and minimally guided self-help, compared to the control group. Additional positive effects were observed for night sweats frequency, mood, sleep and HRQOL.

In another UK-based study (MENOS 1 trial] [58], 96 BC survivors were randomized to group-based CBT or a control group. Approximately half of these BC survivors experienced treatment-induced menopausal symptoms, while the other women were either peri- or postmenopausal at time of BC diagnosis. Similar to the previous study, significantly greater reductions in perceived impact of HF/NS were observed for women allocated to the group-based CBT program at both short- and longer-term follow-up, when compared to the usual care group. For both of these MENOS trials, additional analyses were conducted to investigate whether changes in HF/NS beliefs and behaviors (see Table 1) mediated the observed treatment effects [61, 62]. In BC survivors, changes in all three categories of unhelpful thoughts (i.e. 'hot flushes in social context', 'night sweats and sleep' and 'coping and control'), mediated reductions in perceived impact of HF/NS following CBT [61]. This supported the hypothesis that the development of healthier beliefs contributes to lowering the perceived impact of HF/NS. Changes in the latter two belief categories were also reported to mediate treatment effects in healthy women with menopausal symptoms [62]. Additionally, decreased psychological distress and improved sleep mediated treatment effects in the BC sample. Although in both studies significantly greater improvements in coping behaviors were observed for the CBT groups when compared to the control group, this was not found to mediate treatment effects. Lastly, Chilcot and colleagues [61] found that BC survivors who did not undergo chemotherapy, were non-white and who experienced higher levels of HF/NS at baseline benefited most from the CBT program.

The third RCT, conducted by Duijts et al. in the Netherlands Cancer Institute, was focused on BC survivors with treatment-induced menopausal symptoms [59]. In total, 422 women were randomized to a group-based CBT program, physical exercise, a combination of both or a waiting list control group. All intervention groups reported significantly greater reductions in overall levels of menopausal symptoms as compared to the control group. Furthermore, compared to the control group, the two groups including CBT reported significantly greater reductions in the perceived impact of

HF/NS. A subsequent cost-effectiveness analysis demonstrated that CBT was the most cost-effective intervention, with an incremental cost-utility ratio of € 22.502 per quality adjusted life year (QALY), which is well below the generally accepted threshold of € 30.000/QALY [63]. However, this trial encountered noteworthy problems with compliance, with more than 50% of the participants attending less than 4 of the 6 group sessions. Scheduling and practical conflicts served as the main barriers to attending the group sessions. Per protocol analyses suggested that, if compliance could be increased, the CBT would be even more (cost) effective [59].

**Table 1.** Overview of premises of the experience of HF/NS as incorporated in the CBT program

| **Information input** |
|---|
| Overall stress levels can impact the thermoneutral zone. By reducing overall stress levels, the physiological threshold for HF/NS can be raised. Furthermore, about half of the HF/NS are precipitated by known modifiable triggers, like certain types of food or rushing. |
| **Symptom perception** |
| Detection and attribution processes can influence symptom perception. Overall stress levels can in turn impact these processes. By reducing overall stress levels, shifting attentional focus and improving accurate attribution, women are less likely to over-report symptoms. |
| **Cognitive appraisal** |
| The most important and influential beliefs are 1] the belief that hot flushes are embarrassing and that others will judge them when experiencing hot flushes in a social context, 2] the belief that they cannot influence the extent to which night sweats impact negatively on sleep and daily functioning, and 3] the belief that they are unable to cope with or control hot flushes. These beliefs can be positively influenced by cognitive restructuring exercises. |
| **Behavioral reactions** |
| The most important and influential behaviors are 1] positive coping behaviors like relaxation, and 2] avoidance behaviors, like leaving social situations when experiencing a hot flush. Behavioral experiments can be used to increase positive and decrease negative coping behaviors. |

Abbreviations: HF/NS, hot flushes / night sweats.

The compliance levels and program efficacy might be increased by using a different mode of program delivery. For example, findings from the study by Ayers et al. [60] indicated that minimally guided self-help CBT is also very

effective in reducing the perceived impact of HF/NS. In addition, the same minimally guided self-help format, but with telephone instead of face-to-face guidance, also proved effective in reducing the impact of HF/NS in healthy women with menopausal symptoms [64]. However, it remained unclear whether these minimally guided self-help formats are also effective for BC survivors.

## INTERNET-BASED INTERVENTIONS

Internet-based CBT represent a potentially more viable alternative to the more traditional face-to-face setting and static self-help booklets. Internet-based health interventions are more accessible and convenient, and thus can help minimize scheduling and practical barriers [65, 66]. In addition, many studies have demonstrated the efficacy of Internet-based interventions for the treatment of a range of psychosocial and somatic problems (e.g. depression, anxiety, fatigue) in the general population and in cancer survivors [67-71]. Moreover, the observed strength of the effects tends to be comparable to those reported for face-to-face therapy [66, 72, 73].

Internet-based interventions can be delivered with varying degrees of therapist support. In general, guided Internet-based interventions have been associated with stronger effects than self-managed internet-based interventions. This is primarily attributed to the lower compliance rates associated with the latter format [68, 74, 75]. Internet-based formats increase the reach of an intervention, are less expensive, and represent a promising approach to improving treatment compliance and thus the efficacy of behavioral interventions [76-78].

Two-thirds of BC patients believe that Internet-based therapy can be as effective as face-to-face therapy in improving physical and mental health [79]. The BC survivors included in the Dutch group-based CBT program aimed at reducing menopausal symptom burden [59], indicated an interest and willingness to follow the CBT program via the Internet.

To date, only one (published) study has investigated the efficacy of an Internet-based intervention for women with HF/NS [80]. This study aimed to evaluate the efficacy of guided Internet-based relaxation for hot flushes in healthy, post-menopausal women. The intervention was based on a face-to-face program [81] and consisted of 10 modules. Prior to the start of the intervention, women received a telephone intake and thereafter weekly

online feedback by the same therapist. Halfway through the inclusion period, the RCT was prematurely terminated due to very low compliance rates. Unfortunately, the intervention had not been pilot-tested, which might have provided some indication of potential problems with compliance, and ways in which the program might be adjusted to improve compliance. The authors also suggested that more careful screening, emphasizing the required time investment from the potential participants, could have altered the course of the trial.

Given the success of Internet-based CBT interventions for other health problems, we believed that a better designed trial of an Internet variant of a CBT program for BC survivors that had already been successfully evaluated in more conventional formats (face-to-face; written self-help) was warranted.

## OBJECTIVE AND RESEARCH QUESTIONS

In this thesis, we report the results of a randomized controlled trial that evaluated the efficacy and cost-effectiveness of Internet-based CBT (iCBT), with and without therapist support, for BC survivors with treatment-induced menopausal symptoms. We address the following research questions:

1. What is the efficacy of the iCBT program, with and without therapist support, in alleviating menopausal symptom burden, and other psychosocial outcomes in BC survivors with treatment-induced menopausal symptoms?
2. What is the cost-utility, cost-effectiveness and budget impact of the iCBT program, with and without therapist support, aimed at alleviating menopausal symptom burden in BC survivors with treatment-induced menopausal symptoms?
3. What are the moderators and mediators of the observed treatment effects in BC survivors with treatment-induced menopausal symptoms?

## THESIS OUTLINE

In Chapter 2 we describe the development and evaluation of the beta version of the guided iCBT program. Chapter 3 describes the rationale, design and

methods of the large scale RCT. In Chapter 4 we report on the efficacy of the iCBT program, with and without therapist support, in reducing the perceived impact of HF/NS, overall levels of menopausal symptoms and other psychosocial outcomes in BC survivors with treatment-induced menopausal symptoms. Chapter 5 reports the results of a cost-utility, cost-effectiveness and budget impact analysis of both formats of the iCBT program. In Chapter 6 we investigate who benefits most from the iCBT program and how treatment effects are achieved. This thesis ends with a general discussion of the main findings, methodological considerations, and implications (Chapter 7) and an overall summary (Chapter 8).

## REFERENCES


[1] Nederlandse Kankerregistratie (NKR). <http://www.cijfersoverkanker.nl/>, 2018 (accessed 10 January 2018.2018).

[2] I.K.N. (IKNL), Kankerzorg in beeld: over leven met en na kanker. <https://www.iknl.nl/docs/default-source/shop-downloads/kib-2019.pdf?sfvrsn=3>, 2019 2019).

[3] C.L. Shapiro, A. Recht, Side effects of adjuvant treatment of breast cancer., N Engl J Med 344(26) (2001) 1997-2008.

[4] P.A. Ganz, J.H. Rowland, K. Desmond, B.E. Meyerowitz, G.E. Wyatt, Life after breast cancer: Understanding women's health-related quality of life and sexual functioning, Journal of Clinical Oncology 16(2) (1998) 501-514.

[5] N.K. Aaronson, V. Mattioli, O. Minton, J. Weis, C. Johansen, S.O. Dalton, I.M. Verdonck-de Leeuw, K.D. Stein, C.M. Alfano, A. Mehnert, A. de Boer, L.V. van de Poll-Franse, Beyond treatment - Psychosocial and behavioural issues in cancer survivorship research and practice, EJC supplements : EJC : official journal of EORTC, European Organization for Research and Treatment of Cancer ... [et al.] 12(1) (2014) 54-64.

[6] M. van Leeuwen, O. Husson, P. Alberti, J.I. Arraras, O.L. Chinot, A. Costantini, A.S. Darlington, L. Dirven, M. Eichler, E.B. Hammerlid, B. Holzner, C.D. Johnson, M. Kontogianni, T.K. Kjaer, O. Morag, S. Nolte, A. Nordin, A. Pace, M. Pinto, K. Polz, J. Ramage, J.C. Reijneveld, S. Serpentini, K.A. Tomaszewski, V. Vassiliou, I.M. Verdonck-de Leeuw, I. Vistad, T.E. Young, N.K. Aaronson, L.V. van de Poll-Franse, Understanding the quality of life (QOL) issues in survivors of cancer: towards the development of an EORTC QOL cancer survivorship questionnaire, Health and quality of life outcomes 16(1) (2018) 114.

[7] L.B. Wenzel, D.L. Fairclough, M.J. Brady, D. Cella, K.M. Garrett, B.C. Kluhsman, L.A. Crane, A.C. Marcus, Age-related differences in the quality of life of breast carcinoma patients after treatment, Cancer 86(9) (1999) 1768-74.

[8] N.E. Avis, B. Levine, M.J. Naughton, D.L. Case, E. Naftalis, K.J. Van Zee, Explaining age-related differences in depression following breast cancer diagnosis and treatment, Breast Cancer Res Treat 136(2) (2012) 581-91.

[9] J. Howard-Anderson, P.A. Ganz, J.E. Bower, A.L. Stanton, Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review, J Natl Cancer Inst 104(5) (2012) 386-405.

[10] S. Ahmad, K. Fergus, M. McCarthy, Psychosocial issues experienced by young women with breast cancer: the minority group with the majority of need, Current opinion in supportive and palliative care 9(3) (2015) 271-8.

[11] J. Bines, D.M. Oleske, M.A. Cobleigh, Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer, J Clin Oncol 14(5) (1996) 1718-1729.

[12] S.M. Rosenberg, A.H. Partridge, Premature menopause in young breast cancer: effects on quality of life and treatment interventions, J Thorac Dis 5(Suppl 1) (2013) S55-S61.

[13] P.J. Goodwin, M. Ennis, K.I. Pritchard, M. Trudeau, N. Hood, Risk of menopause during the first year after breast cancer diagnosis., J Clin Oncol 17(8) (1999) 2365-2370.
[14] M.S. Hunter, E.A. Grunfeld, S. Mittal, P. Sikka, A.J. Ramirez, I. Fentiman, H. Hamed, Menopausal symptoms in women with breast cancer: prevalence and treatment preferences., Psychooncology 13(11) (2004) 769-778.
[15] J.S. Carpenter, M.A. Andrykowski, Menopausal symptoms in breast cancer survivors., Oncol Nurs Forum 26(8) (1999) 1311-1317.
[16] P. Gupta, D.W. Sturdee, S.L. Palin, K. Majumder, R. Fear, T. Marshall, I. Paterson, Menopausal symptoms in women treated for breast cancer: the prevalence and severity of symptoms and their perceived effects on quality of life, Climacteric 9(1) (2006) 49-58.
[17] J.R. Bloom, S.L. Stewart, S. Chang, P.J. Banks, Then and now: quality of life of young breast cancer survivors, Psychooncology 13(3) (2004) 147-160.
[18] R.J. Couzi, K.J. Helzlsouer, J.H. Fetting, Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes toward estrogen replacement therapy., J Clin Oncol 13(11) (1995) 2737-2744.
[19] J.S. Carpenter, M.A. Andrykowski, M. Cordova, L. Cunningham, J. Studts, P. McGrath, D. Kenady, D. Sloan, R. Munn, Hot flashes in postmenopausal women treated for breast carcinoma - Prevalence, severity, correlates, management, and relation to qualify of life, Cancer 82(9) (1998) 1682-1691.
[20] J.L. Marino, C.M. Saunders, L.I. Emery, H. Green, D.A. Doherty, M. Hickey, Nature and severity of menopausal symptoms and their impact on quality of life and sexual function in cancer survivors compared with women without a cancer history, Menopause 21(3) (2014) 267-74.
[21] N.E. Avis, S. Crawford, J. Manuel, Psychosocial problems among younger women with breast cancer, Psychooncology 13(5) (2004) 295-308.
[22] Z. Moon, M.S. Hunter, R. Moss-Morris, L.D. Hughes, Factors related to the experience of menopausal symptoms in women prescribed tamoxifen, J Psychosom Obstet Gynaecol 38(3) (2017) 226-235.
[23] T.I. Barron, R. Connolly, K. Bennett, J. Feely, M.J. Kennedy, Early discontinuation of tamoxifen: a lesson for oncologists, Cancer 109(5) (2007) 832-839.
[24] C.C. Murphy, L.K. Bartholomew, M.Y. Carpentier, S.M. Bluethmann, S.W. Vernon, Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review, Breast Cancer Res Treat 134(2) (2012) 459-78.
[25] S.R. Davis, M. Panjari, P.J. Robinson, P. Fradkin, R.J. Bell, Menopausal symptoms in breast cancer survivors nearly 6 years after diagnosis, Menopause 21(10) (2014) 1075-81.
[26] M.E. Schmidt, J. Wiskemann, K. Steindorf, Quality of life, problems, and needs of disease-free breast cancer survivors 5 years after diagnosis, Qual Life Res 27(8) (2018) 2077-2086.
[27] A. Mehnert, U. Koch, Psychological comorbidity and health-related quality of life and its association with awareness, utilization, and need for psychosocial support in a cancer register-based sample of long-term breast cancer survivors, J Psychosom Res 64(4) (2008) 383-91.

[28] R.A. Willems, C.A. Bolman, I. Mesters, I.M. Kanera, A.A. Beaulen, L. Lechner, Cancer survivors in the first year after treatment: the prevalence and correlates of unmet needs in different domains, Psychooncology 25(1) (2016) 51-7.
[29] R.R. Freedman, Pathophysiology and treatment of menopausal hot flashes, Seminars in reproductive medicine 23(2) (2005) 117-25.
[30] J.S. Carpenter, State of the science: Hot flashes and cancer, part 1: Definition, scope, impact, physiology, and measurement, Oncol. Nurs. Forum 32(5) (2005) 959-968.
[31] R.R. Freedman, Menopausal hot flashes: mechanisms, endocrinology, treatment, The Journal of steroid biochemistry and molecular biology 142 (2014) 115-20.
[32] R.A. Anderson, K. Skorupskaite, J. Sassarini, The neurokinin B pathway in the treatment of menopausal hot flushes, Climacteric 22(1) (2019) 51-54.
[33] R.F.M. Vermeulen, M.V. Beurden, C.M. Korse, G.G. Kenter, Impact of risk-reducing salpingo-oophorectomy in premenopausal women, Climacteric 20(3) (2017) 212-221.
[34] A. Benshushan, N. Rojansky, M. Chaviv, S. Arbel-Alon, A. Benmeir, T. Imbar, A. Brzezinski, Climacteric symptoms in women undergoing risk-reducing bilateral salpingo-oophorectomy, Climacteric 12(5) (2009) 404-409.
[35] M.S. Hunter, J.R. Haqqani, An investigation of discordance between subjective and physiological measures of vasomotor symptoms, Climacteric 14(1) (2011) 146-151.
[36] E. Mann, M.S. Hunter, Concordance between self-reported and sternal skin conductance measures of hot flushes in symptomatic perimenopausal and postmenopausal women: a systematic review, Menopause-J. N. Am. Menopause Soc. 18(6) (2011) 709-722.
[37] M.S. Hunter, K.L.M. Liao, A psychological analysis of menopausal hot flushes, Br. J. Clin. Psychol. 34 (1995) 589-599.
[38] M.S. Hunter, E. Mann, A cognitive model of menopausal hot flushes and night sweats, J Psychosom Res 69(5) (2010) 491-501.
[39] E. Stefanopoulou, M.S. Hunter, Symptom perception in healthy menopausal women: Can we predict concordance between subjective and physiological measures of vasomotor symptoms?, American journal of human biology : the official journal of the Human Biology Council 26(3) (2014) 389-94.
[40] P.K. Morrow, D.N. Mattair, G.N. Hortobagyi, Hot flashes: a review of pathophysiology and treatment modalities, Oncologist 16(11) (2011) 1658-1664.
[41] A.H. Boekhout, A.D. Vincent, O.B. Dalesio, J. van den Bosch, J.H. Foekema-Tons, S. Adriaansz, S. Sprangers, B. Nuijen, J.H. Beijnen, J.H. Schellens, Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: a randomized, double-blind, placebo-controlled trial, J Clin Oncol 29(29) (2011) 3862-3868.
[42] C.L. Loprinzi, J. Sloan, V. Stearns, R. Slack, M. Iyengar, B. Diekmann, G. Kimmick, J. Lovato, P. Gordon, K. Pandya, T. Guttuso, Jr., D. Barton, P. Novotny, Newer antidepressants and gabapentin for hot flashes: an individual patient pooled analysis, J Clin Oncol 27(17) (2009) 2831-2837.

[43] L. Holmberg, H. Anderson, HABITS (hormonal replacement therapy after breast cancer--is it safe?), a randomised comparison: trial stopped, Lancet 363(9407) (2004) 453-455.
[44] D. Stan, C.L. Loprinzi, K.J. Ruddy, Breast cancer survivorship issues, Hematology/oncology clinics of North America 27(4) (2013) 805-27, ix.
[45] H.D. Nelson, K.K. Vesco, E. Haney, R. Fu, A. Nedrow, J. Miller, C. Nicolaidis, M. Walker, L. Humphrey, Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis, Jama 295(17) (2006) 2057-71.
[46] K.J. Pandya, G.R. Morrow, J.A. Roscoe, H. Zhao, J.T. Hickok, E. Pajon, T.J. Sweeney, T.K. Banerjee, P.J. Flynn, Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial, Lancet 366(9488) (2005) 818-824.
[47] J.B. Hervik, T. Stub, Adverse effects of non-hormonal pharmacological interventions in breast cancer survivors, suffering from hot flashes: A systematic review and meta-analysis, Breast Cancer Res Treat 160(2) (2016) 223-236.
[48] J.K. Prague, W.S. Dhillo, Neurokinin 3 receptor antagonism - the magic bullet for hot flushes?, Climacteric 20(6) (2017) 505-509.
[49] J.K. Prague, R.E. Roberts, A.N. Comninos, S. Clarke, C.N. Jayasena, P. Mohideen, V.H. Lin, T.P. Stern, N. Panay, M.S. Hunter, L.C. Webber, W.S. Dhillo, Neurokinin 3 receptor antagonism rapidly improves vasomotor symptoms with sustained duration of action, Menopause (2018).
[50] E. Stefanopoulou, E.A. Grunfeld, Mind-body interventions for vasomotor symptoms in healthy menopausal women and breast cancer survivors. A systematic review, J Psychosom Obstet Gynaecol (2016) 1-16.
[51] C. van Driel, A.S. Stuursma, M.J. Schroevers, M. Mourits, G.H. de Bock, Mindfulness, cognitive behavioural and behaviour-based therapy for natural and treatment-induced menopausal symptoms: a systematic review and meta-analysis, BJOG : an international journal of obstetrics and gynaecology (2018).
[52] N. Biglia, V.E. Bounous, F. De Seta, S. Lello, R.E. Nappi, A.M. Paoletti, Non-hormonal strategies for managing menopausal symptoms in cancer survivors: an update, Ecancermedicalscience 13 (2019) 909.
[53] A.J. Vincent, Management of menopause in women with breast cancer, Climacteric 18(5) (2015) 690-701.
[54] J. Carpenter, M.L.S. Gass, P.M. Maki, K.M. Newton, J.V. Pinkerton, M. Taylor, W.H. Utian, P.F. Schnatz, A.M. Kaunitz, M. Shapiro, J.L. Shifren, H.N. Hodis, S.A. Kingsberg, J.H. Liu, G. Richard-Davis, N. Santoro, L.L. Sievert, I. Schiff, C. Pike, P. Allen, Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society, Menopause-J. N. Am. Menopause Soc. 22(11) (2015) 1155-1174.
[55] M.S. Hunter, K.L.M. Liao, Evaluation of a four-session cognitive-behavioural intervention for menopausal hot flushes, Br. J. Health Psychol. 1 (1996) 113-125.
[56] L.C. Swartzman, R. Edelberg, E. Kemmann, Impact of stress on objectively recorded menopausal hot flushes and on flush report bias, Health psychology : official journal of the Division of Health Psychology, American Psychological Association 9(5) (1990) 529-45.

[57] M. Hunter, Cognitive behavioural interventions for premenstrual and menopausal symptoms, Journal of Reproductive and Infant Psychology 21(3) (2003) 183-193.
[58] E. Mann, M.J. Smith, J. Hellier, J.A. Balabanovic, H. Hamed, E.A. Grunfeld, M.S. Hunter, Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial, Lancet Oncol 13(3) (2012) 309-318.
[59] S.F.A. Duijts, M. Van Beurden, H.S.A. Oldenburg, M.S. Hunter, J.M. Kieffer, M.M. Stuiver, M.A. Gerritsma, M.B.E. Menke-Pluymers, P.W. Plaisir, H. Rijna, A.M.F. Lopes Cardozo, G.J. Timmers, S. Van der Meij, H. Van der Veen, N. Bijker, L.M. De Widt-Levert, M.M. Geenen, G. Heuff, E.J. Van Dulken, E. Boven, N.K. Aaronson, Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: Results of a randomized controlled multicenter trial., Journal of Clinical Oncology 30(33) (2012) 4124-4133.
[60] B. Ayers, M. Smith, J. Hellier, E. Mann, M.S. Hunter, Effectiveness of group and self-help cognitive behavior therapy in reducing problematic menopausal hot flushes and night sweats (MENOS 2): a randomized controlled trial, Menopause 19(7) (2012) 749-759.
[61] J. Chilcot, S. Norton, M.S. Hunter, Cognitive behaviour therapy for menopausal symptoms following breast cancer treatment: Who benefits and how does it work?, Maturitas 78(1) (2014) 56-61.
[62] S. Norton, J. Chilcot, M.S. Hunter, Cognitive-behavior therapy for menopausal symptoms (hot flushes and night sweats): moderators and mediators of treatment effects, Menopause-J. N. Am. Menopause Soc. 21(6) (2014) 574-578.
[63] J.C. Mewes, L.M. Steuten, S.F. Duijts, H.S. Oldenburg, M. van Beurden, M.M. Stuiver, M.S. Hunter, J.M. Kieffer, W.H. van Harten, N.K. Aaronson, Cost-effectiveness of cognitive behavioral therapy and physical exercise for alleviating treatment-induced menopausal symptoms in breast cancer patients, Journal of cancer survivorship : research and practice 9(1) (2015) 126-35.
[64] E. Stefanopoulou, M.S. Hunter, Telephone-guided Self-Help Cognitive Behavioural Therapy for menopausal symptoms, Maturitas 77(1) (2014) 73-7.
[65] Y. Leykin, S.M. Thekdi, D.M. Shumay, R.F. Munoz, M. Riba, L.B. Dunn, Internet interventions for improving psychological well-being in psycho-oncology: review and recommendations, Psychooncology 21(9) (2012) 1016-25.
[66] G. Andrews, P. Cuijpers, M.G. Craske, P. McEvoy, N. Titov, Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: a meta-analysis, PLoS One 5(10) (2010) e13196.
[67] A. Barak, L. Hen, M. Boniel-Nissim, N.a. Shapira, A Comprehensive Review and a Meta-Analysis of the Effectiveness of Internet-Based Psychotherapeutic Interventions, Journal of Technology in Human Services 26(2-4) (2008) 109-160.
[68] V. Spek, P. Cuijpers, I. Nyklicek, H. Riper, J. Keyzer, V. Pop, Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis, Psychol Med 37(3) (2007) 319-28.

[69] P. Cuijpers, A. van Straten, G. Andersson, Internet-administered cognitive behavior therapy for health problems: A systematic review., J. Behav. Med. Vol.31(2) (2008) 169-177.
[70] G. Andersson, Using the Internet to provide cognitive behaviour therapy, Behav. Res. Ther. 47(3) (2009) 175-180.
[71] K.E. Post, J. Flanagan, Web based survivorship interventions for women with breast cancer: An integrative review, European Journal of Oncology Nursing 25 (2016) 90-99.
[72] P. Carlbring, G. Andersson, P. Cuijpers, H. Riper, E. Hedman-Lagerlof, Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: an updated systematic review and meta-analysis, Cogn Behav Ther 47(1) (2018) 1-18.
[73] G. Andersson, P. Cuijpers, P. Carlbring, H. Riper, E. Hedman, Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis, World psychiatry : official journal of the World Psychiatric Association (WPA) 13(3) (2014) 288-95.
[74] B. Palmqvist, P. Carlbring, G. Andersson, Internet-delivered treatments with or without therapist input: does the therapist factor have implications for efficacy and cost?, Expert review of pharmacoeconomics & outcomes research 7(3) (2007) 291-7.
[75] H. Baumeister, L. Reichler, M. Munzinger, J. Lin, The impact of guidance on Internet-based mental health interventions — A systematic review, Internet Interventions 1(4) (2014) 205-215.
[76] G. Alkhaldi, F.L. Hamilton, R. Lau, R. Webster, S. Michie, E. Murray, The Effectiveness of Prompts to Promote Engagement With Digital Interventions: A Systematic Review, Journal of medical Internet research 18(1) (2016) 14.
[77] G. Alkhaldi, K. Modrow, F. Hamilton, K. Pal, J. Ross, E. Murray, Promoting Engagement With a Digital Health Intervention (HeLP-Diabetes) Using Email and Text Message Prompts: Mixed-Methods Study, Interactive journal of medical research 6(2) (2017) e14.
[78] N. Titov, B.F. Dear, L. Johnston, C. Lorian, J. Zou, B. Wootton, J. Spence, P.M. McEvoy, R.M. Rapee, Improving adherence and clinical outcomes in self-guided internet treatment for anxiety and depression: randomised controlled trial, PLoS One 8(7) (2013) e62873.
[79] J.E. Owen, J.C. Klapow, D.L. Roth, L. Nabell, D.C. Tucker, Improving the effectiveness of adjuvant psychological treatment for women with breast cancer: The feasibility of providing online support, Psycho-Oncol. 13(4) (2004) 281-292.
[80] L. Lindh-Astrand, A.C.S. Holm, G. Sydsjo, G. Andersson, P. Carlbring, E. Nedstrand, Internet-delivered applied relaxation for vasomotor symptoms in postmenopausal women: Lessons from a failed trial, Maturitas 80(4) (2015) 432-434.
[81] L. Lindh-Astrand, E. Nedstrand, Effects of applied relaxation on vasomotor symptoms in postmenopausal women: a randomized controlled trial, Menopause 20(4) (2013) 401-8.

CHAPTER 2

# AN INTERNET-BASED COGNITIVE BEHAVIORAL THERAPY FOR TREATMENT-INDUCED MENOPAUSAL SYMPTOMS IN BREAST CANCER SURVIVORS: RESULTS OF A PILOT STUDY



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## ABSTRACT

### Purpose

Previous studies demonstrated that a cognitive behavioral therapy (CBT) program delivered in group sessions is effective in alleviating treatment-induced menopausal symptoms in women with breast cancer, but also that in-person CBT is inconvenient for some women and can result in low levels of program compliance. A promising, alternative approach is to use the internet to make this form of CBT more accessible and feasible for patients. The objective of this study was to evaluate the feasibility and to generate preliminary data on the efficacy of a guided, Internet-based CBT program.

### Methods

Twenty-one patients with treatment-induced menopausal symptoms started the guided Internet-based CBT program. Self-report questionnaires were completed at baseline and 10 weeks (post-treatment). Counselors' evaluations were obtained via interviews. Primary outcomes were program usage, compliance rates and patient and counselor satisfaction. Secondary outcomes were overall levels of endocrine symptoms and hot flush/night sweats (HF/NS) problem rating.

### Results

Ninety percent of patients completed the program as planned. Satisfaction rates were high among patients and counselors. Small revisions to the program were advised. There was a significant decrease over time in overall levels of endocrine symptoms and HF/NS problem rating.

### Conclusion

These findings suggest that an Internet-based CBT program for women with treatment-induced menopausal symptoms is feasible and promising in terms of efficacy. The efficacy of the CBT program is currently being investigated in a larger randomized controlled trial.

## INTRODUCTION

Treatment-induced menopause is a major concern for younger women undergoing treatment for breast cancer [1]. Menopausal symptoms include hot flushes and night sweat (HF/NS), vaginal dryness, decreased libido, dysuria, urinary incontinence, insomnia, dyspareunia, weight gain and psychological distress [2, 3]. Among these menopausal symptoms, hot flushes are considered the most disruptive and most prevalent problem, with prevalence rates varying between 63–85% [2, 4-6]. Menopausal symptoms can cause discomfort and adversely affect health-related quality of life (HRQOL) [1-7].

Menopausal symptoms can be treated by hormone therapy (HT) and by non-hormonal (clonidine, gabapentin, selective serotonin reuptake inhibitors) medications [8]. Hormonal therapy is contraindicated for women with a history of breast cancer and non-hormonal treatment modalities can have bothersome side effects [8-10]. In addition many breast cancer survivors indicate a preference for nonmedical treatment of their menopausal symptoms [4].

Based on their model of menopause-related HF/NS, Hunter and Liao [11] developed a cognitive behavioral therapy (CBT) program to decrease the impact of HF/NS on women's lives. The CBT program incorporates information about symptoms, monitoring and modifying precipitants, relaxation and stress management, cognitive restructuring of unhelpful assumptions and automatic thoughts and encouraging helpful behavioral strategies to promote the development of helpful cognitive and behavioral coping styles [12]. Three randomized controlled trials (RCTs) have demonstrated the efficacy of a group-based version of this CBT program in reducing menopausal complaints in women in the general population and in women with menopausal symptoms after breast cancer treatment [13-15]. In the Dutch trial [15], noteworthy problems with compliance in the CBT group were observed, with more than 50% of the participants attending less than two-thirds of the planned sessions. Commonly reported reasons for noncompliance were scheduling conflicts related to work and transportation/distance to the session site. Duijts et al. [15] suggested that compliance might be increased by creating more flexible session hours. Flexibility can also be increased by offering a different mode of delivery.

Findings from both Ayers et al. [13] and Stefanopoulou and Hunter [16] indicate that a guided, that is, face-to-face or telephone-based, self-management (booklet) version of the CBT is also very effective in reducing menopausal complaints in women with naturally occurring menopausal symptoms. Results of the latter study suggest that guidance via telephone contact might be as effective as face-to-face contact. However, it is unclear whether guided self-management is an effective approach for breast cancer survivors.

A more contemporary alternative to self-management programs offered in book(let) form is an Internet-based program. There is growing evidence that guided Internet-based CBT is an effective method to treat a range of psychosocial problems in both the general population and in cancer survivors [17-21]. Internet-based CBT programs are generally highly acceptable, accessible and efficient [20]. Women who had participated in the Dutch trial noted above [15], expressed an interest and willingness to undergo a CBT program administered via the Internet.

We took a stepwise approach to developing the guided Internet-based CBT program, "EVA-Online". The content of the program was based on an in-person CBT program originally developed by Hunter and colleagues [11, 22] that had been adapted to the Dutch setting [15]. Additionally, we adapted the form and content of the program so that it would be suitable for delivery via the Internet. We did this in collaboration with Myra Hunter, healthcare professionals involved in the original RCT of the in-person version of the program [15], and Minddistrict, a company specialized in the development of online healthcare interventions. A beta version of the program was administered to a small group of women and evaluated for user friendliness and comprehensibility. This resulted in minor changes to both the program content and procedures. It is the revised version of the program that was used in the current pilot study.

The aim of the current study was to pilot test the resulting Internet-based CBT program for women experiencing breast cancer treatment-induced menopausal symptoms. Primary assessment included the use of and compliance with the program, and patients' and counselors' satisfaction with the program. In addition, an initial, very preliminary evaluation of its effect on overall levels of endocrine symptoms and, in particular, the impact on HF/NS was carried out.

# METHODS

## Study sample

The patient sample consisted of 21 women with histologically confirmed primary breast cancer who were 53 years or younger and premenopausal at time of diagnosis, and had received adjuvant chemotherapy and/or oophorectomy and/or hormonal therapy (including current use for hormonal therapy only). Chemotherapy and oophorectomy had to be completed at least 4 months and no longer than 5 years before study entry. Inclusion criteria were hot flushes, night sweats and/or vaginal dryness sometimes (two symptoms) or often (one symptom) during the previous two weeks. Women were excluded from the study if they lacked basic proficiency in Dutch, had serious overt cognitive or psychiatric problems, or were participating in concurrent studies or rehabilitation programs focused on the reduction of or coping with menopausal symptoms.

## Recruitment and procedures

Women were invited to participate in the study through advertisements on cancer-related websites. Women who responded by e-mail received detailed information about the study and were requested to fill out a short screening questionnaire. When initial eligibility criteria were met, women were contacted by telephone to confirm their eligibility, to explain the Internet-based program and the study procedures, and to confirm their willingness to invest the requisite time and effort. A baseline questionnaire and informed consent form were sent to eligible and motivated patients. In consultation with the local Institutional Review Board (IRB), it was determined that due to the pilot nature of this study, approval of the IRB was not necessary but informed consent was required. All women who participated in the study provided written informed consent.

## The guided Internet-based cognitive behavioral therapy program

The primary focus of the Internet-based CBT program is on HF/NS. Other problems concerning stress, sexuality and weight gain are also addressed. Throughout the program, women are encouraged to develop helpful cognitive and behavioral coping styles. The program consists of 6 modules, which preferably should be followed during 6 consecutive weeks. The first 5 modules cover the following topics: introduction to breast cancer and menopause, hot flushes, stress and relaxation, improving sleep and body

image/sexuality. In the last module, participants are asked to reflect on the previous modules, and to write a maintenance plan. Each module consists of psycho-education, assignments and homework assignments. The written information is accompanied by video clips of experts (a breast cancer surgeon and a sexologist) who provide complementary information to that provided in the written text. Also, incorporated into the program are short video clips and written text of women who had gone through treatment-induced menopause and had followed the program. The written text also provided examples of how to complete the homework assignments.

Each participant was assigned a counselor, who first conducted a 30-minute telephone interview and subsequently provided weekly, written feedback based on the completed homework assignments. The contact between the counselor and the women was by e-mail. The three counselors involved in the study were two medical social workers and a psychologist trained in the use of the program. The average time investment for the participants throughout the 6-week program period was approximately 1 hour per week to complete a module and 30 minutes per day for homework assignments (e.g. keeping a daily hot flush/night sweats diary and doing relaxation exercises).

## Data collection

All participants were asked to complete self-report questionnaires before (T0) and shortly after (T1) completing (or discontinuing) the program. A reminder was sent to participants who did not return the questionnaires within 1 week. Those who did not return a completed questionnaire after the written reminder were contacted once by phone, if possible.

## Study measures

### *Sociodemographic and clinical data*

The participants' age, marital status, educational level, work status and type and time since completion of breast cancer treatment were obtained via the screening and baseline questionnaires.

## Primary outcomes

### *Program usage and compliance*

Usage of the CBT program was defined as the number of modules completed and time spent (in weeks) on completing the entire program. Completion of the first three modules was considered as an acceptable level of program

compliance because these modules form the core of the CBT program. The usage data were based on electronic logs and information obtained from the counselors.



***Participants' evaluation of the intervention***

Upon completion of the program, participants were asked to complete a short evaluation questionnaire that included statements about their satisfaction with different elements of the program as assessed on a 5-point Likert scale ranging from 'strongly disagree' to 'strongly agree'. In total, 11 statements were presented regarding prior information provision (two items: 'sufficient information about the treatment approach' and 'sufficient information about the expected treatment results'), therapist experience (four items regarding 'expertise', 'trustworthiness', 'respectfulness', and 'interest'), experienced effect (two items: 'progress made' and 'control over symptoms'), content (one item: 'satisfaction with modules'), usability (one item: 'easy to use'), general approach (one item: 'correct approach for symptoms'). Participants were also asked if they would recommend the program to other women experiencing treatment-induced menopausal symptoms and to give a grade between 0 (very poor) to 10 (excellent) to the overall program.

***Counselors' evaluation of the intervention***

When all treatments were completed, interviews were held with the counselors during which they were asked to provide their opinions about the program (content and procedures).

## Secondary outcomes

***Overall levels of menopausal symptoms and hot flushes / night sweats problem rating***

The secondary outcomes were the overall levels of endocrine symptoms, as assessed by the 18-item endocrine subscale of the Functional Assessment of Cancer Therapy questionnaire (FACT-ES) [23] and the impact of HF/NS as defined as problem ratings of three items of the Hot Flush Rating scale (HFRS) [24]. The FACT-ES has been demonstrated to have good face, content, and discriminant validity [23]. The questionnaire has been used successfully in studies of breast cancer patients treated with tamoxifen [23], of women at increased risk of breast/ovarian cancer who had undergone prophylactic oophorectomy [25], and in our previous study of breast cancer

survivors with treatment-induced menopausal symptoms [15]. The scale has shown high levels of reliability (Cronbach's alphas > 0. 80 in all studies). The HFRS problem rating scale has good internal consistency (Cronbach α = 0.90) and test-retest reliability across a 2-3 week period (r = 0.80), and has been used in breast cancer patients treated with tamoxifen [4] and in three studies evaluating the efficacy of CBT for either breast cancer treatment-induced or naturally occurring menopausal symptoms [13-15]. A change of 0.5 standard deviation on the FACT-ES scale [26] and a 2-point change on the problem rating scale of the HFRS were considered as clinically significant [14].

### Statistical analysis

Descriptive statistics (means, SDs, and percentages) were used to characterize the study sample, and to display the scores on the outcome variables. Paired Student's *t* tests were used to compare baseline scores to postprogram scores on the FACT-ES and the HFRS problem rating scale. A p-value of 0.05 was considered statistically significant. Effect sizes (ES) were calculated using Cohen's d statistic, with an effect size of 0.2 considered as small, 0.5 as moderate, and 0.8 as large [27]. All analyses were conducted using the Statistical Packages for the Social Sciences (SPSS), version 21.0.

## RESULTS

### Sample characteristics

Demographic and clinical characteristics of the sample are shown in Table 1. In total, 21 women participated in the study. Participants had a mean age of 47.0 years (SD = 3.94), 81% had a partner and 76% were employed. Seventeen women had been treated with chemotherapy, three had received an oophorectomy, and 20 were still undergoing hormonal therapy.

### Program usage and compliance

Nineteen of the 21 women completed all six program modules. One participant discontinued after completing two modules because she was dissatisfied with the content, and the other participant discontinued after four modules because of psychological problems. The participants needed, on average, 6.5 weeks (SD = 1.3 weeks) to complete the program.

**Table 1.** Sociodemographic and clinical characteristics

| | No. of patients | % |
|---|---|---|
| Age in years | | |
| Mean (SD) | 47.0 (3.94) | |
| Marital status | | |
| Single | 3 | 14.2 |
| Married/partner | 17 | 81.0 |
| Divorced | 1 | 4.8 |
| Education | | |
| High school | 2 | 9.5 |
| Vocational education | 8 | 38.1 |
| College/University | 11 | 52.4 |
| Employment | | |
| Full-time | 3 | 14.3 |
| Part-time | 13 | 61.9 |
| On work disability | 3 | 14.3 |
| Other | 2 | 9.5 |
| Chemotherapy | 17 | 81.0 |
| Time since completion* | | |
| < 1 year | 6 | 35.3 |
| 1 – 3 years | 8 | 47.1 |
| < 3 years | 2 | 11.8 |
| Hormonal therapy | 20 | 95.2 |
| Ongoing | 20 | 100 |
| Type of hormonal therapy** | | |
| Tamoxifen | 14 | 70.0 |
| Arimidex | 3 | 15.0 |
| Letrozol | 1 | 5.0 |
| Oophorectomy | 3 | 14.3 |
| Time since completion | | |
| 1 – 3 years ago | 3 | 100 |

*1 missing case.
**2 missing cases.

## Participants' evaluation of the intervention

Evaluation data (n = 18) are provided in Table 2. All women reported having received sufficient information about the program's approach (100%) and most women reported that they received sufficient information about the expected results of the program (94%). All qualities of the counselor, that is, 'expertise', 'trustworthiness', 'respectfulness' and 'interest' were positively evaluated (percent of positive responses ranging per item between approximately 89% and 95%).Seventy-eight percent of the women reported that they had made sufficient progress and 83% reported feeling more control over their symptoms after completing the program. Additionally, most women were satisfied with the online modules (88.8%), the user-friendliness of the program (94.4%), and thought the treatment was the correct approach for their symptoms (83.3%). Although one woman consistently evaluated the program elements as unsatisfactory, and some women occasionally provided a neutral or negative response, most women (94.4%) would advise others to follow the program. Four women provided supplementary comments; two reported that they found the feedback from the counselor to be too brief and too general, and another two women commented on the amount of time and effort needed to complete the program. Overall, the participants were very positive about the program ([Mean = 8.3, SD = 1.33] on a 10-point scale ranging from 1 to 10; higher score is more positive).

## Counselors' evaluation of the program

The counselors were generally satisfied with the content of the program, but suggested to add an extra cognitive assignment to better balance the behavioral and cognitive parts of the program. They also suggested including a "re-cap" at the beginning of every module in which the participants are asked to reflect on their progress in the past week. They indicated that by doing so, they would have more information on which they could base their weekly, personalized feedback.

## Overall levels of endocrine symptoms and hot flushes / night sweats problem rating

There was a clinically significant improvement over time in the overall levels of endocrine symptoms as assessed by the FACT-ES ($p < 0.001$, d = 1.09) and in HF/NS problem rating as assessed by the HFRS problem rating scale ($p < 0.001$, d = 1.60). The percentage of women reporting a

**Table 2.** Participants' evaluation of the program

| | % (Strongly) Disagree | % Neither agree nor disagree | % (Strongly) agree |
|---|---|---|---|
| Information | | | |
| I received sufficient information about the treatment approach | - | - | 100 |
| I received sufficient information about the expected treatment results | 5.6 | - | 94.4 |
| Counselor | | | |
| I think the counselor had sufficient expertise | 5.6 | 5.6 | 88.8 |
| I can trust the counselor | - | 16.7 | 83.3 |
| The counselor was respectful | - | 5.6 | 94.4 |
| I think the counselor was interested in me and my opinion | - | 5.6 | 94.4 |
| Experienced effect | | | |
| Because of the treatment I have made sufficient progress | 5.6 | 16.7 | 77.7 |
| Because of the treatment I have more control over my symptoms | 5.6 | 11.1 | 83.3 |
| Other | | | |
| I am satisfied with the online modules | 5.6 | 5.6 | 88.8 |
| I think the online program was easy to use | - | 5.6 | 94.4 |
| I think the treatment is the correct approach for my symptoms | 5.6 | 11.1 | 83.3 |
| I would advise others to follow this treatment | 5.6 | - | 94.4 |

**Table 3.** Preliminary results: program effects on menopausal symptoms

| | T0 | | | T1 | | | Difference between T0-T1 | |
|---|---|---|---|---|---|---|---|---|
| | No. of patients | Mean | SD | No. of patients | Mean | SD | *p* | ES |
| FACT-ES | 21 | 44.5 | 6.89 | 18 | 53.3 | 8.55 | <.001 | 1.09 |
| HFRS problem rating | 21 | 4.6 | 1.51 | 18 | 2.5 | 1.32 | <.001 | 1.60 |

Abbreviations: FACT-ES, Functional Assessment of Cancer Therapy–Endocrine Subscale; HFRS, Hot Flush Rating Scale, problem rating subscale; T0, baseline assessment; T1, posttreatment assessment.

clinically significant improvement over time was 72% and 61% for the FACT-ES and the HFRS problem rating scale, respectively.

## DISCUSSION

The aim of this study was to evaluate the feasibility of an Internet-based CBT program (EVA-Online) and to provide preliminary data on its impact on overall levels of endocrine symptoms and the impact of HF/NS in women who had experienced treatment-induced menopausal symptoms.

Ninety percent of the patients completed the full program. This contrasts strongly with the much lower program completion rate (58%) observed in the original EVA trial, in which an in-person group version of the CBT program was used [15]. The majority of women were (very) satisfied with the program. Comments made by both the women and the counselors highlighted the importance of prior screening and information provision in order to provide realistic expectations regarding the time and effort required by the program, and the need to provide/receive more detailed feedback, when necessary. This has led to some additional, minor changes in the program.

The preliminary efficacy data suggest that the Internet-based program has a strong positive impact on the overall levels of endocrine symptoms and the impact of HF/NS. Over 70% of the participants reported a clinically significantly improvement in overall levels of endocrine symptoms and over 60% in impact of HF/NS. This is in line with findings of the previous studies of the, in-person and telephone-based versions of the program [13-16].

We would emphasize that these results need to be interpreted with caution because of the small sample size, the absence of a control group, and the limited follow-up. However, the results were sufficiently promising to justify conducting a RCT, which we are currently doing [28]. We expect the results of this trial to be available in 2018.

In conclusion, our findings indicate that EVA-online is a feasible and potentially efficacious intervention to reduce endocrine symptoms and the impact of HF/NS in women who have experienced premature menopause as a result of their treatment for breast cancer. Results of our ongoing RCT will provide more definitive information regarding the efficacy of this intervention.

## REFERENCES


[1] N.E. Avis, S. Crawford, J. Manuel, Psychosocial problems among younger women with breast cancer, Psychooncology 13(5) (2004) 295-308.

[2] R.J. Couzi, K.J. Helzlsouer, J.H. Fetting, Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes toward estrogen replacement therapy., J Clin Oncol 13(11) (1995) 2737-2744.

[3] N. Biglia, M. Cozzarella, F. Cacciari, R. Ponzone, R. Roagna, F. Maggiorotto, P. Sismondi, Menopause after breast cancer: a survey on breast cancer survivors, Maturitas 45(1) (2003) 29-38.

[4] M.S. Hunter, E.A. Grunfeld, S. Mittal, P. Sikka, A.J. Ramirez, I. Fentiman, H. Hamed, Menopausal symptoms in women with breast cancer: prevalence and treatment preferences., Psychooncology 13(11) (2004) 769-778.

[5] P. Gupta, D.W. Sturdee, S.L. Palin, K. Majumder, R. Fear, T. Marshall, I. Paterson, Menopausal symptoms in women treated for breast cancer: the prevalence and severity of symptoms and their perceived effects on quality of life, Climacteric 9(1) (2006) 49-58.

[6] J.S. Carpenter, D. Johnson, L. Wagner, M. Andrykowski, Hot flashes and related outcomes in breast cancer survivors and matched comparison women, Oncol Nurs Forum 29(3) (2002) E16-25.

[7] J. Howard-Anderson, P.A. Ganz, J.E. Bower, A.L. Stanton, Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review, J Natl Cancer Inst 104(5) (2012) 386-405.

[8] D. Stan, C.L. Loprinzi, K.J. Ruddy, Breast cancer survivorship issues, Hematology/oncology clinics of North America 27(4) (2013) 805-27, ix.

[9] L. Holmberg, H. Anderson, HABITS (hormonal replacement therapy after breast cancer--is it safe?), a randomised comparison: trial stopped, Lancet 363(9407) (2004) 453-455.

[10] H.D. Nelson, K.K. Vesco, E. Haney, R. Fu, A. Nedrow, J. Miller, C. Nicolaidis, M. Walker, L. Humphrey, Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis, Jama 295(17) (2006) 2057-71.

[11] M.S. Hunter, K.L.M. Liao, Evaluation of a four-session cognitive-behavioural intervention for menopausal hot flushes, Br. J. Health Psychol. 1 (1996) 113-125.

[12] M. Hunter, Cognitive behavioural interventions for premenstrual and menopausal symptoms, Journal of Reproductive and Infant Psychology 21(3) (2003) 183-193.

[13] B. Ayers, M. Smith, J. Hellier, E. Mann, M.S. Hunter, Effectiveness of group and self-help cognitive behavior therapy in reducing problematic menopausal hot flushes and night sweats (MENOS 2): a randomized controlled trial, Menopause 19(7) (2012) 749-759.

[14] E. Mann, M.J. Smith, J. Hellier, J.A. Balabanovic, H. Hamed, E.A. Grunfeld, M.S. Hunter, Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial, Lancet Oncol 13(3) (2012) 309-318.

[15] S.F.A. Duijts, M. Van Beurden, H.S.A. Oldenburg, M.S. Hunter, J.M. Kieffer, M.M. Stuiver, M.A. Gerritsma, M.B.E. Menke-Pluymers, P.W. Plaisir, H. Rijna, A.M.F. Lopes Cardozo, G.J. Timmers, S. Van der Meij, H. Van der Veen, N. Bijker, L.M. De Widt-Levert, M.M. Geenen, G. Heuff, E.J. Van Dulken, E. Boven, N.K. Aaronson, Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: Results of a randomized controlled multicenter trial., Journal of Clinical Oncology 30(33) (2012) 4124-4133.
[16] E. Stefanopoulou, M.S. Hunter, Telephone-guided Self-Help Cognitive Behavioural Therapy for menopausal symptoms, Maturitas 77(1) (2014) 73-7.
[17] A. Barak, L. Hen, M. Boniel-Nissim, N. Shapira, A comprehensive review and a meta-analysis of the effectiveness of Internet-based psychotherapeutic interventions., Journal of Technology in Human Services Vol.26(2-4) (2008) 109-160.
[18] V. Spek, P. Cuijpers, I. Nyklicek, H. Riper, J. Keyzer, V. Pop, Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis, Psychol Med 37(3) (2007) 319-28.
[19] G. Andersson, Using the Internet to provide cognitive behaviour therapy, Behav Res Ther 47(3) (2009) 175-180.
[20] Y. Leykin, S.M. Thekdi, D.M. Shumay, R.F. Munoz, M. Riba, L.B. Dunn, Internet interventions for improving psychological well-being in psycho-oncology: review and recommendations, Psycho-Oncol. 21(9) (2012) 1016-1025.
[21] P. Cuijpers, A. van Straten, G. Andersson, Internet-administered cognitive behavior therapy for health problems: A systematic review., J. Behav. Med. Vol.31(2) (2008) 169-177.
[22] M.S. Hunter, E. Mann, A cognitive model of menopausal hot flushes and night sweats, J Psychosom Res 69(5) (2010) 491-501.
[23] L.J. Fallowfield, S.K. Leaity, A. Howell, S. Benson, D. Cella, Assessment of quality of life in women undergoing hormonal therapy for breast cancer: validation of an endocrine symptom subscale for the FACT-B, Breast Cancer Res Treat 55(2) (1999) 189-199.
[24] M.S. Hunter, K.L.M. Liao, A psychological analysis of menopausal hot flushes, Br. J. Clin. Psychol. 34 (1995) 589-599.
[25] J.B. Madalinska, J. Hollenstein, E.M.A. Bleiker, M. van Beurden, H.B. Valdimarsdottir, L.F. Massuger, K.N. Gaarenstroom, M.J.E. Mourits, R.H.M. Verheijen, E.B.L. van Dorst, H. van der Putten, J. van der Velden, H. Boonstra, N.K. Aaronson, The quality of life effects of prophylactic salpingo-oophorectomy versus gynecologic screening among women at increased risk of hereditary ovarian cancer, J Clin Oncol. 23(28) (2005) 6890-98.
[26] D.L. Streiner, G.R. Norman, J. Cairney, Health measurement scales: a practical guide to their development and use, 5th ed., Oxford University Press Oxford, UK, 2014.
[27] J. Cohen, Statistical power analysis for the behavioral sciences, Lawrence Earlbaum Associates, Hillsdale, New Jersey, 1988.
[28] V. Atema, M. Van Leeuwen, H.S. Oldenburg, V. Retél, M. Van Beurden, M.S. Hunter, N.K. Aaronson, Design of a randomized controlled trial of Internet-based cognitive behavioral therapy for treatment-induced menopausal symptoms in breast cancer survivors BMC Cancer (In press ).

CHAPTER 3

# DESIGN OF A RANDOMIZED CONTROLLED TRIAL OF INTERNET-BASED COGNITIVE BEHAVIORAL THERAPY FOR TREATMENT-INDUCED MENOPAUSAL SYMPTOMS IN BREAST CANCER SURVIVORS



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# ABSTRACT

## Purpose

Menopausal symptoms are common and may be particularly severe in younger women who undergo treatment-induced menopause. Medications to reduce menopausal symptoms are either contra-indicated or have bothersome side effects. Previous studies have demonstrated that face-to-face cognitive behavioral therapy (CBT) is effective in alleviating menopausal symptoms in women with breast cancer. However, compliance with face-to-face CBT programs can be problematic. A promising approach is to use the Internet to make this form of CBT more accessible and feasible for patients. This study is evaluating the efficacy and cost-effectiveness of on an Internet-based CBT program, with or without therapist guidance, in alleviating or reducing the severity of menopausal symptoms.

## Methods

In a multicenter, randomized controlled trial we are evaluating the efficacy of two Internet-based CBT programs in alleviating or reducing the impact of menopausal symptoms, and particularly hot flushes and night sweats, in breast cancer survivors who have experienced a treatment-induced menopause. Secondary outcomes include sexual functioning, sleep quality, hot flush frequency, psychological distress and health-related quality of life and cost-effectiveness. We will recruit 248 women who will be randomized to either a therapist guided or a self-management version of the 6-week Internet-based CBT program, or to a usual care, waiting list control group. Self-administered questionnaires are completed at baseline (T0), and at 10 weeks (T1) and 24 weeks (T2) post-randomization.

## Conclusion

Internet-based CBT is a potentially useful treatment for reducing menopausal symptoms in breast cancer survivors. This study will provide evidence on the efficacy and cost-effectiveness of such an Internet-based CBT program, with or without therapist support. If demonstrated to be efficacious and cost-effective, the availability of such structured supportive intervention programs will be a welcome addition to standard medical treatment offered to cancer patients with treatment-induced menopause.

## INTRODUCTION

Breast cancer is the most common cancer among women worldwide, with approximately 1,7 million new cases reported in 2012 [1]. Due to increasing numbers of patients with cancer and improving survival rates more interest and research has focused on health-related quality of life (HRQOL) of breast cancer survivors, including treatment-induced menopausal symptoms [2]. Nearly 25% of all women with breast cancer are premenopausal at time of diagnosis [3]. Breast cancer treatment, including chemotherapy and endocrine treatment induce premature menopause, either by damaging the ovaries or altering the uptake of estrogen [4, 5]. Oophorectomy also results in surgically induced menopause [6, 7].

Premature menopause is a major concern of younger women undergoing treatment for breast cancer [8]. Primary menopausal symptoms include hot flushes, night sweats, vaginal dryness, decreased libido, dysuria and urinary incontinence. Secondary symptoms include insomnia due to night sweats, dyspareunia because of vaginal dryness, weight gain, and psychological distress [4, 9, 10]. Among these menopausal symptoms, hot flushes are considered to be the most disruptive, with prevalence rates between 63% and 85% in breast cancer survivors [9, 11-14]. Hot flushes are often more severe in women who experience treatment-induced menopause, compared to women going through natural menopause [7, 15, 16]. The exact etiology of hot flushes is not fully understood. They appear to be the result of a dysfunction in the thermoregulatory system via the hypothalamus, due to (natural or treatment-induced) changes in estrogen levels. Together with changes in the neurotransmitters serotonin and norepinephrine they impact the thermoregulatory homeostasis [17-19].

Menopausal symptoms are an important source of morbidity and discomfort in breast cancer patients and survivors, and they may also adversely affect women's sexual functioning and overall HRQOL [8, 20-26]. Moreover, menopausal symptoms are an important reason why some women discontinue endocrine treatment [27-29]. Many women experiencing treatment-induced menopause report unmet needs for information about how to manage menopausal symptoms [30].

Menopausal symptoms can be treated medically by either hormone replacement therapy (HRT) or non- hormonal treatment modalities including clonidine, selective serotonin reuptake inhibitors (SSRI's) and gabapentin [31, 32]. Although highly effective in alleviating menopausal

symptoms, HRT is contra-indicated in women with a history of breast cancer [33, 34]. Non-hormonal treatments are moderately effective but have a range of common and bothersome side-effects [35-39]. Many breast cancer survivors with treatment-induced menopause prefer non-medical treatments for their menopausal symptoms [14].

There is increasing evidence that behavioral interventions have a positive impact on symptoms experienced by women with naturally occurring and treatment-induced menopause [40-46]. Cognitive behavioral therapy (CBT) is the only type of behavioral intervention with level 1 efficacy evidence for both women with naturally occurring and treatment-induced menopause. Use of CBT has been recommended by the North American Menopause Society [47].

Hunter and colleagues [48] developed a cognitive model of menopausal hot flushes to explain symptom perception, cognitive appraisal, and behavioral reactions to symptoms. Based on this model, they developed a form of CBT, including relaxation and psycho-education, that focuses on the relationships between thoughts, feelings and behavior [49]. Their CBT intervention incorporates information about symptoms, monitoring and modifying precipitants, relaxation and stress management, cognitive restructuring of unhelpful assumptions and automatic thoughts, and encouraging helpful behavioral strategies [40].

Three randomized controlled trials (RCT's) have demonstrated the efficacy of this CBT program in reducing menopausal complaints in women from the general population and in women with menopausal symptoms after breast cancer treatment [42-44]. In the study of Ayers and colleagues [42], 140 women from the general population were randomly assigned to group CBT, guided self-help CBT or a no treatment control group. Both CBT groups decreased significantly in hot flush and night sweat (HF/NS) problem ratings compared to the control group 6 weeks and 6 months after randomization. These findings in the general population, however, cannot necessarily be generalized to cancer patients. Women who go through natural menopause have much greater opportunities to communicate with and relate to their same-aged peers who have gone through or are going through menopause. Cancer patients distinguish themselves from women who go through natural menopause by the severity of their symptoms, and the typically younger age at which they experience treatment-induced menopause.

In the study of Mann et al. [43] 96 breast cancer survivors with problematic menopausal HF/NS were randomly assigned to either group CBT or usual

care. In this study, women who had received CBT had significantly reduced HF/NS problem rating as compared to the control group at 9 weeks and at 6 months post-randomization. Our group [44] conducted a 4-group RCT (the EVA trial) to evaluate the efficacy of group CBT, physical exercise, or a combination of CBT and physical exercise in alleviating treatment-induced menopausal symptoms in breast cancer survivors, as compared to a waiting list control group (WLC) (N=422). All intervention groups reported a significant decrease in levels of endocrine symptoms 12 weeks and 6 months after randomization, compared to the usual care waiting list control group. The two groups that included CBT also reported a significant decrease in HF/NS problem rating at 12 weeks and 6 months. However, in the RCT of Duijts and colleagues [44], noteworthy problems were observed in compliance with the group CBT. More than 50% of women attended less than 4 of the 6 CBT sessions. Many women reported scheduling conflicts related to work and childcare as the reason for their under-compliance. Per-protocol analysis suggested that, if compliance rates could be increased, the intervention would be even more effective. Many women indicated an interest and willingness to undergo a CBT program administered via the Internet. This was viewed as a more flexible alternative to face-to-face group CBT, and thus is hypothesized to result in increased compliance and increased efficacy of the treatment. Further, two-thirds of breast cancer patients believe that Internet-based therapy is equally or more likely to result in improved physical and mental health, as compared to face-to-face therapy [50].

A cost-effectiveness analysis (CEA) of the EVA-trial data showed that CBT was likely to be the most cost-effective intervention, with incremental cost-utility ratios of € 22,502 per quality adjusted life year (QALY) for CBT versus WLC and € 28,078 / QALY for physical exercise versus WLC [51]. Providing CBT via an Internet-based platform, either in a guided or self-managed format may further increase the cost-effectiveness of this intervention.

There is growing evidence that Internet-based CBT is an effective method to treat a range of psychosocial problems in both the general population and in cancer survivors [52-56]. The overall mean effect size of (ES) of Internet-based therapy is 0.53 which is comparable to the average ES of traditional face-to-face therapy [57, 58]. In general, Internet-based interventions with therapist guidance have been found to be more effective then Internet-based interventions without any therapist guidance [53, 54, 56]. However, self-management interventions have clear benefits in terms of accessibility

and convenience, and lower costs. For these reasons, increasing attention is being paid to optimizing self-management variants of CBT programs and to identifying who may benefit most from them [59-62]. For example, it has been argued that self-managed interventions are more effective with motivated patients who have moderate rather than severe symptoms [63, 64].

Self-managed interventions are often associated with low compliance rates. However, this can be improved when the self-management interventions include prior screening and are part of a 'closed system' (i.e. not accessible without some form of eligibility check) [59-61]. Under such conditions, compliance rates are similar to those found in face-to face therapy [60]. There is also evidence that compliance in self-management interventions can be further increased by the use of reminders [65-67].

This randomized, controlled, multicenter trial, "EVA-Online", is designed to evaluate the efficacy and cost-effectiveness of two Internet-based CBT programs, one guided and the other self-managed, to reduce or ameliorate treatment-induced menopausal symptoms in women who have had breast cancer. We hypothesize that women in both Internet-based CBT groups will report a significantly greater reduction in overall levels of menopausal symptoms and/or HF/NS problem rating than women in the control group. Secondarily, we hypothesize that women in both Internet-based CBT groups will report significantly greater improvement in sexual functioning, sleep quality, hot flush and night sweats frequency, psychological distress and HRQOL than women in the control group. We will also evaluate the relative efficacy of self-managed versus guided Internet-based CBT, but this will be done in a more descriptive manner, given that the trial is not powered to test these differences formally. We are also investigating, in a more exploratory manner, the extent to which program compliance serves as a predictor, and hot flush beliefs and behavior as mediators of the treatment effects on the primary outcomes of interest [68]. Finally, we hypothesize that both Internet-based CBT groups have a higher probability of being cost-effective compared to the control group. If demonstrated to be efficacious and cost-effective, the availability of such structured supportive intervention programs will be a welcome addition to standard medical treatment offered to cancer survivors with treatment-induced menopause.

# METHODS

In this trial, patients are randomized to one of three study arms. There are two interventions arms, i.e. Internet-based guided CBT and Internet-based self-management CBT, and one waiting list control arm. The design of the trial and the anticipated flow of the participants are displayed in Figure 1. This trial protocol (June 25th, 2015, version 2) has been approved by the Institutional Review Board (IRB) of the Netherlands Cancer Institute (under number NL 53182.031.15), as well as by the review boards of all hospitals from which patients are being recruited. Any important protocol modifications (not anticipated) will be reported to the IRB and the trail registration (clinicaltrials.gov).



## Study sample

The study sample will be composed of 248 women, 50 years of age or younger at time of diagnosis, with histologically confirmed primary breast cancer (stages: T1 – T4, N0 – N3 and M0). All women will have been premenopausal at the time of diagnosis, and will have experienced a treatment-induced menopause due to (neo) adjuvant chemotherapy and/or hormonal therapy and/or oophorectomy. In case of treatment-induced menopause due to (neo) adjuvant chemotherapy or oophorectomy, treatment should have been completed a minimum of 4 months and a maximum of 5 years prior to study entry (with the exception of Herceptin use). Women may currently be receiving adjuvant hormonal therapy. All women should be disease-free at time of study entry. Potentially eligible women are screened for the presence of problematic HF/NS during the past 2 months. They must have experienced at least 10 hot flushes or night sweats during the past week and these HF/NS should be experienced as problematic (as indicated by an average score of 2 or higher on three items of the Hot Flush Rating Scale [69]).

Women are excluded from the study if they lack basic proficiency in Dutch, have been treated in the past for another form of cancer (other than basal cell carcinoma), have serious overt cognitive or psychiatric problems that would preclude them from following the intervention or completing the study questionnaires, or have no Internet access. Patients participating in concurrent studies or rehabilitation programs focused on the reduction of or coping with menopausal symptoms (i.e. relaxation, mindfulness, psycho-education and /or CBT) are also excluded.

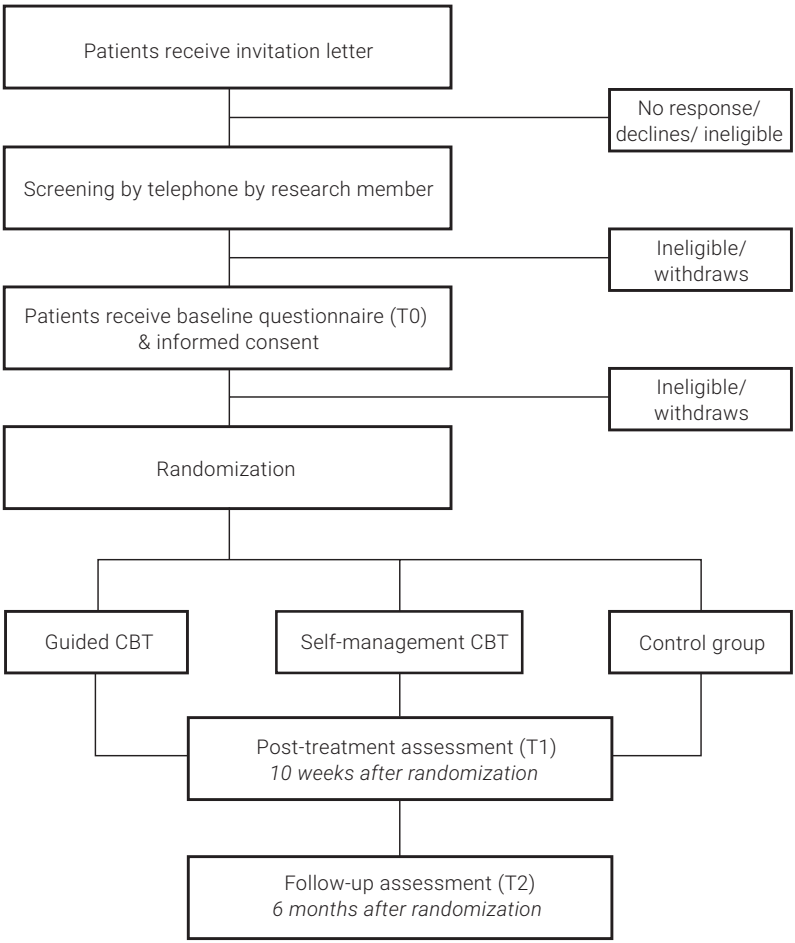


**Figure 1.** Overview of overall trial design
Abbreviations: CBT, cognitive behavioral therapy; T0, baseline assessment; T1 post-treatment assessment; T2, follow-up assessment.

## Recruitment and randomization

We are recruiting patients from 13 community and university hospitals in the Netherlands. We identify potentially eligible patients through hospital registries and the database of the Netherlands Cancer Registry. Potentially eligible patients are sent a personalized letter by their treating physician informing them about the study and the Internet-based program. Women are asked to respond to this invitation by returning either a short screening questionnaire (when there is interest in participating), or a postcard indicating reasons for declining participation. Non-respondents are sent a reminder 2 weeks after the first invitation.

The women who express interest in the study, but do not meet the eligibility criteria receive a personalized letter that explains why they are not eligible. When initial eligibility criteria are met, women are contacted by telephone to confirm their eligibility, to explain the Internet-based program and the RCT, and to confirm their willingness to invest the requisite time and effort if they are randomized to either of the two intervention groups. A baseline questionnaire and informed consent form are sent to eligible and motivated patients. Upon return of both to the study staff, patients are randomized to the guided Internet-based CBT group (n = 83) the self-management Internet-based CBT group (n = 83) or to a usual care, 'waiting list' control group (n = 82) using the minimization technique [70] with age (< 40 years; 40 – 45 years, > 45 years), current endocrine treatment for breast cancer (yes; no), time since chemotherapy (< 1 year; 1 – 3 years; > 3 years) and current use of non-hormonal treatments for hot flushes (antidepressants, clonidine, gabapentin; yes; no) as stratification variables. Due to the nature of the study, blinding is not possible.

## Study arms

All participants randomized to either of the two intervention groups receive access to the same Internet-based CBT program. The primary focus of the program is on HF/NS, with participants being encouraged to develop helpful cognitive and behavioral coping styles. Other problem areas, including sexuality, weight gain and stress are also addressed by the program. The CBT program, is based on the work of Hunter and colleagues [40, 42, 49, 71] and has been tailored for use by breast cancer survivors [43, 44]. The program consists of six modules, which preferably should be followed in six consecutive weeks (for a description of the program see Table 1). Each module contains the following sections: reflection on

progress in past week, an introduction, psycho-education, and in-session and homework assignments. Video clips of experts (a breast surgeon and a sexologist) provide complementary information to that presented in the written text. Also incorporated in the program are testimonials (short video clips and written text) of women who have gone through treatment-induced menopause and who have followed the program. The written text also provides examples of how to complete the homework assignments. The six modules are presented in a sequential order, wherein each module builds upon the previous one. The average estimated time investment is one hour a week to complete a module and 30 minutes per day for homework (e.g. keeping a daily hot flush/night sweats diary and relaxation exercises).

***Intervention group: guided Internet-based cognitive behavioral therapy program***

The women in the guided Internet-based CBT group receive, in addition to the online CBT program, a scheduled 30 minute telephone interview prior to the start of the program and weekly feedback per email during the course of the program. After receiving and reading the weekly feedback, participants are given access to the next module. The interview and weekly feedback are provided by a trained therapist (medical social worker or psychologist). The therapist has access to the participants' in-session reflection, homework assignments and daily hot flush diary. Participants can also contact the therapist by email if they have any questions. Monitoring of the integrity of the intervention is carried out at regular intervals by the study coordinator.

***Intervention group: self-management Internet-based cognitive behavioral therapy program***

The women in the self-management Internet-based CBT group have access to the online CBT program as described above and receive weekly reminders by email. Participants in this group have access to the entire CBT program from time of enrollment forward, but are advised and encouraged to follow the program using a weekly schedule for 6 consecutive weeks.

***Waiting list control group***

Participants in the waiting list control group are offered the opportunity to follow the CBT program after completion of the 6-month follow-up questionnaire. There are no other behavioral interventions for menopausal symptoms available through the participating hospitals, but women in all

groups are asked at the follow-up assessments if they engaged in any other means to reduce their menopausal symptoms.

**Table 1.** Description of program modules

| |
|---|
| **Module 1 Welcome**<br>• Introduction to the online program<br>• Psycho-education about the effect of breast cancer on menopause, menopausal symptoms and the influence of relaxation<br>• In-session assignment: making a schedule for reading the sessions and doing homework<br>• Homework: keeping a hot flushes and night sweats diary; practicing relaxation techniques |
| **Module 2 Help a hot flush**<br>• Psycho-education about the physiology of HF/NS and the role of thoughts, feelings and behaviors<br>• In-session assignment: recognizing patterns of and triggers for hot flushes; cognitive restructuring of unhelpful thoughts<br>• Homework: as before + monitoring triggers and applying helpful thoughts |
| **Module 3 From stressing to relaxing**<br>• Psycho-education about stress, the relationship between stress and hot flushes, cognitive and behavioral stress management techniques, relaxation<br>• In-session assignment: identification of stressful events, usual reaction to stress and goal setting to reduce stress<br>• Homework: as before + implementation of stress goal |
| **Module 4 Improving sleeping**<br>• Psycho-education about sleep, sleeping problems and how to improve quality of sleep, cognitive and behavioral reactions to sleep problems/night sweats<br>• In-session assignment: sleep hygiene questionnaire, goal setting to improve sleep<br>• Homework: as before + implementation of sleeping goals |
| **Module 5 My body and sexuality**<br>• Psycho-education about sexual problems and weight issues, cognitive and behavioral precipitants and consequences of sexual problems and weight issues<br>• In-session assignment: goal setting for sexual problems (if present) and weight issues (if present)<br>• Homework: as before + implementation of goals |
| **Module 6 Keep progressing**<br>• Psycho-education about the (benefits of) using an action plan<br>• In-session assignment: identification of helpful cognitive and/or behavioral strategies as discussed/learned throughout each module, goal setting for maintenance plan; identification of possible barriers and how to overcome them.<br>• Homework: as before + implementation of maintenance plan |

Abbreviations: HF/NS, hot flushes / night sweats.

## Data Collection

All trial participants complete a battery of self-report questionnaires at equivalent points in time: T0 (at baseline prior to randomization), T1 (10 weeks after randomization) and T2 (6 months after randomization). A reminder is sent to participants who do not return the questionnaire within one week. If a woman does not complete the questionnaire in the week after the reminder, she is contacted by telephone. Every effort is made to obtain a final post-intervention assessment for patients who discontinue the intervention. Additionally, all women, including those in the control group, are asked if, during the period of the study, they had engaged in any (other) activities to alleviate their menopausal symptoms (e.g., contacts with patient self-help groups, use of Internet resources, alternative remedies, etc.).

## Study measures

### *Sociodemographic and clinical data*

The patients' age, education, marital status, living situation, work status, weight and height, medication use (including alternative medications or therapies for menopausal symptoms) and life style variables (e.g. smoking, physical activity/exercise) are obtained via the baseline questionnaire. Clinical information, including date of diagnosis, tumor characteristics, and treatment history are abstracted from the patients' medical records and via self-report. During the follow-up period, participants are asked if they had resumed menstruation and whether they had discontinued endocrine treatment, if applicable.

### *Outcome measures*

A detailed description of the outcome measures is provided in Table 2. Briefly, the primary outcome measures include standardized self-report questionnaires assessing hot flushes and night sweats problem rating using the Hot Flush Problem Rating Scale (HFRS [69]), and overall levels of menopausal symptoms using the Functional Assessment of Cancer Therapy – Endocrine symptom scale (FACT-ES [72]). Secondary outcome measures include standardized self-report questionnaires assessing sexual functioning (SAQ [73]), sleep quality (GSQS [74]); hot flush and night sweats frequency (HFRS [69]), psychological distress (HADS [75, 76]) and health-related quality of life (SF-36 Health Survey [77, 78]).

### *Mediating and process measures*

Beliefs about hot flushes and night sweats are considered mediators of the effect of the CBT program [79]. These are assessed with the Behavior Short-Form HFNS Beliefs and Behavior Scale, a 16 item scale that includes items from the Hot Flush Beliefs Scale [80] and the Hot Flush Behavior Scale [81], (Hunter, personal communication).

### *Compliance with the intervention*

Women are asked to indicate the number of CBT program modules they completed, the frequency with which they did the homework assignments and the total amount of time (in weeks) that they used the program. We are also able to monitor the actual use (frequency and duration) of the online CBT program through log data. We consider completion of the first three modules evidence of an acceptable level of program compliance because these are the modules that specifically focus on the primary outcomes.

Women who do not complete the intervention are asked to indicate their reason(s) for discontinuation (e.g., lack of motivation, illness, program burden). We assess general self-efficacy, social support and intention to complete the program as potential predictors of compliance. General self-efficacy is measured with the General Self-Efficacy Scale [82]. It includes 10 items (4 point Likert scale). Social support is assessed by the emotional/informational support subscale (8 items Cronbach's alpha 0.96) of the Medical Outcome Study- Social Support Scale (MOS-SS [83]). Behavioral intention is assessed by three items (5 point Likert scale) derived from the Theory of Planned Behavior [84].

### *Patients' evaluation of the intervention program*

At T1 (immediate post-intervention), women in both intervention groups are asked to complete a short questionnaire about their experience with the Internet-based CBT program. This will include questions about the perceived efficacy of and satisfaction with the program, whether they would suggest any changes to the program, and if they would recommend it to other women experiencing treatment-induced menopausal symptoms. In addition, in an effort to better understand how the program might be improved, we will conduct telephone interviews (30 minutes) after the T2 assessment with women who indicated on the questionnaire that the intervention did not have the desired effect and/or gave the intervention a low rating and/or would not recommend the program to others.

**Table 2.** Study outcome measures and corresponding questionnaires

| Variable | Questionnaire | Details |
|---|---|---|
| **Primary outcomes** | | |
| Hot flush/ Night sweats problem rating | HFRS | • 3 items (subscale), 10 point scale<br>• Score range: the mean is used, therefore scores between 0 – 10; higher scores indicate higher problem rating<br>• Time frame: 1 week<br>• Test-retest reliability 0.80 |
| Overall level of menopausal symptoms | FACT-ES | • 18 items, 4 point Likert scale<br>• Score range: 0 – 72; higher scores indicate fewer menopausal symptoms<br>• Time frame: 1 week<br>• Cronbach's alpha: >0.80 |
| **Secondary outcomes** | | |
| Sexual functioning | SAQ | • 10 items, 4 point Likert scale<br>• Subscales: pleasure; discomfort; habit<br>• Score range: pleasure 0 – 18 higher scores indicate higher levels of pleasure; discomfort 0 – 6 lower scores indicates lower levels of discomfort; habit 0 – 3; single item (0 'less sexual activity than usual' to 3 'much more sexual activity than usual'<br>• Time frame: past month<br>• Test-retest kappa: 0.50-0.76 |
| Sleep quality | GSQS | • 14 items, dichotomous (yes/no) scale<br>• Score range: 0 – 14; higher scores indicate more sleep problems<br>• Time frame: past month |
| Hot flush frequency | HFRS | • 2 items (subscale); open-ended frequency scale<br>• Score range: reported average of HF/NS per week<br>• Time frame: past week<br>• Test-retest reliability 0.80 |
| Psychological distress | HADS | • 14 items, 4-point Likert scale<br>• Subscales: depression (HADS-D); anxiety (HADS-A)<br>• Score range: total score 0 – 42; subscale scores 0 – 21 higher score indicates more psychological distress<br>• Time frame: past week<br>• Cronbach's alpha: HADS-D 0.67-0.90; HADS-A 0.68-0.93 |

*(Continued on following page)*

**Table 2.** Study outcome measures and corresponding questionnaires (continued)

| Variable | Questionnaire | Details |
|---|---|---|
| Health-related quality of life | SF-36 | • 36 items, dichotomous and 3- to 6-point Likert scales<br>• Subscales: physical functioning, role limitations due to physical health problems, bodily pain, social functioning, general mental health, role limitations due to emotional problems, vitality, general health perceptions<br>• Score range: 0- 100* higher score indicates higher levels of functioning/well-being<br>• Time frame: past week<br>• Cronbach's alpha: 0.66-0.91 (mean 0.84)<br>• For the cost-effectiveness analysis we will map the SF-36 onto the EuroQol5D to obtain utilities |

Abbreviations: FACT-ES, Functional Assessment of Cancer Therapy - Endocrine Symptoms; GSQS, Groningen Sleep Quality Scale; HADS, Hospital Anxiety and Depression Scale; HF/NS, hot flushes/night sweats; HFRS, Hot Flush Rating Scale; SAQ, Sexual Activity Questionnaire; SF-36, Short Form Health Survey.



## Cost-effectiveness

We will perform a cost-effectiveness analysis (CEA) using a validated health economic model as developed for use earlier in the EVA-trial [51]. The cost-effectiveness of the Internet-based guided CBT versus the Internet-based self-management CBT versus usual care will be expressed as: (1) cost per clinically relevant significant reduction on the problem-rating scale of the HFRS and the FACT-ES and (2) cost per QALY gained. A change of at least two points on the ten-point problem-rating scale of the HFRS, and of 0.5 SD on the FACT-ES is considered a relevant improvement [49]. A societal and hospital perspective from the Netherlands, plus a 5 year time horizon will be adopted. Future costs and effects will be discounted at 4% and 1.5%, respectively, according to the Dutch guidelines. A Markov model will be constructed with 3 mutually exclusive health states: "menopausal symptoms", "reduction in menopausal symptoms", and "recurrence". Using a 6-month cycle length, the model will simulate the course of events in a hypothetical cohort of 1000 breast cancer survivors. The "effectiveness" part of the cost-effectiveness equation will be based on the FACT-ES and SF-6D. The SF-6D [85], derived from the SF-36, will be mapped onto the EuroQol-5D, which will provide utilities. With the utilities, the SF-6D allows indirectly generating quality adjusted life years (QALYs) to be used in cost-effectiveness analysis.

For the direct costs, we will ask all women to report at T1 and T2 their use of health care services (e.g., GP, medical specialist, paramedical care etc.), medication use and workdays lost due to illness. In calculating the intervention costs, we will include the time spent by health professionals in providing feedback to participants (where applicable), staff training, administration, and material costs. Detailed descriptions of the intervention will be made to identify specific cost items and corresponding volumes of resource use. Subsequently, costs will be calculated by multiplying unit prices (or appropriate tariffs) by volumes of use, following the Dutch pharmacoeconomics costing guidelines [86].

The indirect costs will be measured by the Friction cost method, which is the period over which the production loss is calculated, i.e. the time that an employer needs to replace a sick employee. The calculation of the average labor costs per working day will be based on the weighted average labor costs of full-time and part-time employed persons in the Netherlands [87].

## Power calculation

The HFRS problem rating scale and the FACT-ES scale score, assessing endocrine symptoms, are the primary outcomes on which sample size calculations are based. With a total sample of 198 women (66 per group), and under the assumption of no interaction, the study will have 80% power to detect a 0.5 standard deviation difference (Cohen's effect size) with a p value of 0.05 (two sided test) [88]. We anticipate that this effect size will be sufficient to demonstrate the efficacy of the interventions, as the CBT group intervention in the EVA-study yielded effect sizes for the primary outcomes of approximately 0.5 [44]. We will recruit 248 women into the study, to allow for an attrition rate of approximately 20% (i.e. women who discontinue participation in the study entirely, including failure to complete follow-up questionnaires). Women who discontinue participation in one of the intervention groups but complete the follow-up assessments will be included in the analysis.

## Statistical analysis

All data will be anonymized prior to final data analysis. The data set will not contain any personal identifiers. Only study staff will have access to these data.

Analyses will first be performed to evaluate the comparability of the intervention groups (guided versus self-management) and control group at

baseline in terms of sociodemographic and clinical characteristics. ANOVA tests or appropriate non-parametric statistics will be used, depending on the level of measurement. If, despite the stratified randomization procedures, the groups are found not to be comparable on one more background variables, those variables will be employed routinely as covariates in subsequent analyses. Questionnaire scores will be calculated according to published scoring algorithms. We will compare both intervention groups with the control group over time using multilevel procedures with repeated measures, using a restricted maximum likelihood (REML) solution to model specific contrasts between groups and follow-up assessment [89]. Within each multilevel model the control group will be the reference category. For the analysis of the secondary outcome measures, appropriate statistical adjustments will be made for multiple testing. Differences in mean change scores over time between the intervention groups and the control group will be accompanied by effect sizes (ES). These effect sizes will be calculated using standard statistical procedures. Effect sizes of approximately 0.5 are considered clinically significant [90]. All analyses will be conducted on an intention to treat (ITT) basis. In addition, per-protocol (PP) analyses will be performed (as a secondary analysis) on patients who met criteria for minimal compliance with the intervention(s). Supplementary analyses will be carried out in which data relating to compliance with the program elements will be taken into account. Specifically, we will determine whether the level of compliance is associated significantly with the change over time in the primary and secondary outcomes. We will also investigate whether program effectiveness varies significantly as a function of changes in hot flush beliefs and behaviors.



### *Cost-effectiveness analysis*

We will use a Markov model to perform an incremental cost-effectiveness and cost-utility analyses. The cost-effectiveness ratio is calculated by dividing the difference between the mean total costs of the intervention and control groups by the difference in mean primary clinical effects of the groups [51]. The incremental cost-utility ratio expresses the additional costs of the intervention per quality-adjusted life year (QALY) gained, compared to the usual care group.

### *Modeling statistics*

State of the art health economic methods will be applied. These include the estimation of the degree of uncertainty about each input parameter and the use of probabilistic sensitivity analyses. Parameter values will be drawn randomly from the assigned distributions, using Monte Carlo simulation with 10,000 iterations. The degree of uncertainty will be illustrated by using confidence intervals for costs and health effects. Scatter-plots, confidence ellipses on cost-effectiveness planes and cost-effectiveness acceptability curves will be presented [91-93]. We will use the European informal ceiling ratio of €30,000 per QALY [86]. Finally, a budget impact analysis will be performed from the perspective of the health care provider.

All study results will be published in peer-reviewed publications and will result in a Ph.D. thesis. Authorship eligibility will be based on the Vancouver Protocol [94]. Participating patients will receive a lay summary of the results.

## DISCUSSION

A relatively large percentage of young breast cancer survivors experience treatment-induced menopausal symptoms, with hot flushes being the most common and severe symptom [9, 11-14]. There is a need for effective and safe non-medical treatment options for these symptoms. Studies show that, both in the general population and among breast cancer survivors, CBT is an effective treatment method for alleviating menopausal symptoms when provided in a group setting or through guided self-help [42-44, 49]. However, compliance can be problematic [44]. A promising approach is to make this form of CBT more accessible and feasible for participants by administering it via the Internet. In the current trial we are evaluating the efficacy and cost-effectiveness of Internet-based CBT in alleviating or reducing menopausal symptoms and HF/NS problem ratings in younger breast cancer survivors who experience treatment-induced menopause. Secondary outcomes include sexual functioning, sleep quality, HF/NS frequency, psychological distress and overall HRQOL.

This trial has several notable strengths, including: (1) the randomized trial design; (2) the multicenter nature of the trial; (3) the comparison of both intervention groups with a waiting- list control group; (4) the use of intention-to-treat analysis; (5) the relatively long-term follow-up; and (6) the inclusion of a cost-effectiveness evaluation.

Several limitations of the trial should also be noted. First, it would be valuable to compare the Internet-based CBT groups with a face-to-face CBT group in order to compare compliance, experience and effectiveness. However, recruitment and follow-up proved to be problematic in our previous group CBT trial (EVA-study) [44]. Also we consider it important to first establish the efficacy of the Internet-based CBT program. Second, we anticipate that both intervention groups (guided and self-management) will be effective, in comparison with the control group. The trial was powered based on the estimated effects of each of the two Internet-based CBT interventions in comparison to the control group. It may also be the case that one of the two CBT programs is more or less effective than the other. One would hope, given the additional costs involved, that the guided CBT program would be more efficacious than the self-management CBT program. However, if such differences exist, the magnitude of difference will likely be smaller than that expected between the CBT programs and the control group. In order to detect a smaller difference (effect size) when comparing the two variants of the CBT program, we would need a substantially larger sample size [88]. Unfortunately, our budget, both in terms of financial resources and time, does not allow us to increase the sample size. Nevertheless, within the limits of statistical power available to us, we will calculate between CBT group differences in both efficacy and cost-effectiveness outcomes. Finally, although women in the waiting list control group will not be provided with any materials or program elements, they might look for other options themselves. However, we do not anticipate that this will take place in a structured or systematic way. In any case, at each assessment point, women are asked to report any activities that they may have undertaken to alleviate their menopausal symptoms.

In conclusion, given the rate and severity of treatment induced menopausal symptoms in breast cancer survivors, there is a need for more easily accessible and efficient CBT interventions for these problems. If demonstrated to be efficacious and cost-effective, the availability of such a structured supportive intervention program will be a welcome addition to standard medical treatment offered to breast cancer survivors. It is anticipated that such a program will have direct benefit in terms of symptom relief and the improvement of patients' HRQL, while making more efficient use of health care resources.

## REFERENCES


[1] I.A.f.R.o. Cancer, GLOBOCAN 2012: Estimated cancer incidence, mortality, and prevalence worldwide in 2012. <http://globocan.iarc.fr/Pages/fact_sheets_population.aspx>, 2012 (accessed April, 1 2016).

[2] M.P. Coleman, D. Forman, H. Bryant, J. Butler, B. Rachet, C. Maringe, U. Nur, E. Tracey, M. Coory, J. Hatcher, C.E. McGahan, D. Turner, L. Marrett, M.L. Gjerstorff, T.B. Johannesen, J. Adolfsson, M. Lambe, G. Lawrence, D. Meechan, E.J. Morris, R. Middleton, J. Steward, M.A. Richards, I.M.W. Grp, Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data, Lancet 377(9760) (2011) 127-138.

[3] A.C. Society., Cancer Facts Figures - 2000., Atlanta, GA, 2003.

[4] J. Bines, D.M. Oleske, M.A. Cobleigh, Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer, J Clin Oncol 14(5) (1996) 1718-1729.

[5] C.L. Shapiro, A. Recht, Side effects of adjuvant treatment of breast cancer., N Engl J Med 344(26) (2001) 1997-2008.

[6] J.B. Madalinska, M. Van Beurden, E.M. Bleiker, H.B. Valdimarsdottir, J. Hollenstein, L.F. Massuger, K.N. Gaarenstroom, M.J. Mourits, R.H. Verheijen, E.B. Van Dorst, H. Van der Putten, K. Van der Velden, H. Boonstra, N.K. Aaronson, The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women after prophylactic salpingo-oophorectomy, J.Clin.Oncol. 24(22) (2006) 3576-3582.

[7] S.M. Rosenberg, A.H. Partridge, Premature menopause in young breast cancer: effects on quality of life and treatment interventions, J Thorac Dis 5(Suppl 1) (2013) S55-S61.

[8] N.E. Avis, S. Crawford, J. Manuel, Psychosocial problems among younger women with breast cancer, Psychooncology 13(5) (2004) 295-308.

[9] R.J. Couzi, K.J. Helzlsouer, J.H. Fetting, Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes toward estrogen replacement therapy., J Clin Oncol 13(11) (1995) 2737-2744.

[10] N. Biglia, M. Cozzarella, F. Cacciari, R. Ponzone, R. Roagna, F. Maggiorotto, P. Sismondi, Menopause after breast cancer: a survey on breast cancer survivors, Maturitas 45(1) (2003) 29-38.

[11] J.R. Bloom, S.L. Stewart, S. Chang, P.J. Banks, Then and now: quality of life of young breast cancer survivors, Psychooncology 13(3) (2004) 147-160.

[12] J.S. Carpenter, M.A. Andrykowski, M. Cordova, L. Cunningham, J. Studts, P. McGrath, D. Kenady, D. Sloan, R. Munn, Hot flashes in postmenopausal women treated for breast carcinoma - Prevalence, severity, correlates, management, and relation to qualify of life, Cancer 82(9) (1998) 1682-1691.

[13] J.S. Carpenter, M.A. Andrykowski, Menopausal symptoms in breast cancer survivors., Oncol Nurs Forum 26(8) (1999) 1311-1317.

[14] M.S. Hunter, E.A. Grunfeld, S. Mittal, P. Sikka, A.J. Ramirez, I. Fentiman, H. Hamed, Menopausal symptoms in women with breast cancer: prevalence and treatment preferences., Psychooncology 13(11) (2004) 769-778.
[15] C. Crandall, L. Petersen, P.A. Ganz, G.A. Greendale, Association of breast cancer and its therapy with menopause-related symptoms, Menopause 11(5) (2004) 519-530.
[16] A. Benshushan, N. Rojansky, M. Chaviv, S. Arbel-Alon, A. Benmeir, T. Imbar, A. Brzezinski, Climacteric symptoms in women undergoing risk-reducing bilateral salpingo-oophorectomy, Climacteric 12(5) (2009) 404-409.
[17] T.D. Shanafelt, D.L. Barton, A.A. Adjei, C.L. Loprinzi, Pathophysiology and treatment of hot flashes, Mayo Clinic proceedings 77(11) (2002) 1207-18.
[18] R.R. Freedman, Pathophysiology and treatment of menopausal hot flashes, Seminars in reproductive medicine 23(2) (2005) 117-25.
[19] C.H. Mom, C. Buijs, P.H.B. Willemse, M.J.E. Mourits, E.G.E. de Vries, Hot flushes in breast cancer patients, Crit. Rev. Oncol./Hematol. 57(1) (2006) 63-77.
[20] J.B. Madalinska, J. Hollenstein, E.M.A. Bleiker, M. van Beurden, H.B. Valdimarsdottir, L.F. Massuger, K.N. Gaarenstroom, M.J.E. Mourits, R.H.M. Verheijen, E.B.L. van Dorst, H. van der Putten, J. van der Velden, H. Boonstra, N.K. Aaronson, The quality of life effects of prophylactic salpingo-oophorectomy versus gynecologic screening among women at increased risk of hereditary ovarian cancer, J Clin Oncol. 23(28) (2005) 6890-6898.
[21] P.A. Ganz, J.H. Rowland, K. Desmond, B.E. Meyerowitz, G.E. Wyatt, Life after breast cancer: Understanding women's health-related quality of life and sexual functioning, Journal of Clinical Oncology 16(2) (1998) 501-514.
[22] S. YoungMcCaughan, Sexual functioning in women with breast cancer after treatment with adjuvant therapy, Cancer Nurs. 19(4) (1996) 308-319.
[23] A.Y. Rostom, The Management of Menopausal Sequelae in Patients with Breast Cancer, Clinical Oncology 13(3) (2001) 174-180.
[24] J. Howard-Anderson, P.A. Ganz, J.E. Bower, A.L. Stanton, Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review, J Natl Cancer Inst 104(5) (2012) 386-405.
[25] R. Sadovsky, R. Basson, M. Krychman, A.M. Morales, L. Schover, R. Wang, L. Incrocci, Cancer and Sexual Problems, Journal of Sexual Medicine 7(1) (2010) 349-373.
[26] N. Angelopoulos, V. Barbounis, S. Livadas, D. Kaltsas, G. Tolis, Effects of estrogen deprivation due to breast cancer treatment., Endocr Relat Cancer 11(3) (2004) 523-535.
[27] C. Owusu, D.S. Buist, T.S. Field, T.L. Lash, S.S. Thwin, A.M. Geiger, V.P. Quinn, F. Frost, M. Prout, M.U. Yood, F. Wei, R.A. Silliman, Predictors of tamoxifen discontinuation among older women with estrogen receptor-positive breast cancer, J Clin Oncol 26(4) (2008) 549-555.
[28] T.L. Lash, M.P. Fox, J.L. Westrup, A.K. Fink, R.A. Silliman, Adherence to tamoxifen over the five-year course, Breast Cancer Res Treat 99(2) (2006) 215-20.

[29] T.I. Barron, R. Connolly, K. Bennett, J. Feely, M.J. Kennedy, Early discontinuation of tamoxifen: a lesson for oncologists, Cancer 109(5) (2007) 832-839.
[30] D.J. Anderson, P. Yates, A. McCarthy, C.P. Lang, M. Hargraves, N. McCarthy, J. Porter-Steele, Younger and older women's concerns about menopause after breast cancer, Eur J Cancer Care (Engl) 20(6) (2011) 785-794.
[31] A. MacLennan, S. Lester, V. Moore, Oral oestrogen replacement therapy versus placebo for hot flushes (Cochrane Review). The Cochrane Library, 2004.
[32] S.E. Fugate, C.O. Church, Nonestrogen treatment modalities for vasomotor symptoms associated with menopause., Ann Pharmacother 38(9) (2004) 1482-1499.
[33] L. Holmberg, H. Anderson, HABITS (hormonal replacement therapy after breast cancer--is it safe?), a randomised comparison: trial stopped, Lancet 363(9407) (2004) 453-455.
[34] A. Finch, G. Evans, S.A. Narod, BRCA carriers, prophylactic salpingo-oophorectomy and menopause: clinical management considerations and recommendations, Womens Health (Lond Engl) 8(5) (2012) 543-555.
[35] K.J. Pandya, G.R. Morrow, J.A. Roscoe, H. Zhao, J.T. Hickok, E. Pajon, T.J. Sweeney, T.K. Banerjee, P.J. Flynn, Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial, Lancet 366(9488) (2005) 818-824.
[36] A.H. Boekhout, A.D. Vincent, O.B. Dalesio, J. van den Bosch, J.H. Foekema-Tons, S. Adriaansz, S. Sprangers, B. Nuijen, J.H. Beijnen, J.H. Schellens, Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: a randomized, double-blind, placebo-controlled trial, J Clin Oncol 29(29) (2011) 3862-3868.
[37] A. Bardia, P. Novotny, J. Sloan, D. Barton, C. Loprinzi, Efficacy of nonestrogenic hot flash therapies among women stratified by breast cancer history and tamoxifen use: a pooled analysis, Menopause 16(3) (2009) 477-83.
[38] D. Stan, C.L. Loprinzi, K.J. Ruddy, Breast cancer survivorship issues, Hematology/oncology clinics of North America 27(4) (2013) 805-27, ix.
[39] H.D. Nelson, K.K. Vesco, E. Haney, R. Fu, A. Nedrow, J. Miller, C. Nicolaidis, M. Walker, L. Humphrey, Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis, Jama 295(17) (2006) 2057-71.
[40] M. Hunter, Cognitive behavioural interventions for premenstrual and menopausal symptoms, Journal of Reproductive and Infant Psychology 21(3) (2003) 183-193.
[41] J.H. Irvin, A.D. Domar, C. Clark, P.C. Zuttermeister, R. Friedman, The effects of relaxation response training on menopausal symptoms., J Psychosom Obstet Gynaecol 17(4) (1996) 202-207.
[42] B. Ayers, M. Smith, J. Hellier, E. Mann, M.S. Hunter, Effectiveness of group and self-help cognitive behavior therapy in reducing problematic menopausal hot flushes and night sweats (MENOS 2): a randomized controlled trial, Menopause 19(7) (2012) 749-759.

[43] E. Mann, M.J. Smith, J. Hellier, J.A. Balabanovic, H. Hamed, E.A. Grunfeld, M.S. Hunter, Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial, Lancet Oncol 13(3) (2012) 309-318.

[44] S.F.A. Duijts, M. Van Beurden, H.S.A. Oldenburg, M.S. Hunter, J.M. Kieffer, M.M. Stuiver, M.A. Gerritsma, M.B.E. Menke-Pluymers, P.W. Plaisir, H. Rijna, A.M.F. Lopes Cardozo, G.J. Timmers, S. Van der Meij, H. Van der Veen, N. Bijker, L.M. De Widt-Levert, M.M. Geenen, G. Heuff, E.J. Van Dulken, E. Boven, N.K. Aaronson, Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: Results of a randomized controlled multicenter trial., Journal of Clinical Oncology 30(33) (2012) 4124-4133.

[45] P.A. Ganz, G.A. Greendale, L. Petersen, L. Zibecchi, B. Kahn, T.R. Belin, Managing menopausal symptoms in breast cancer survivors: Results of a randomized controlled trial, J. Natl. Cancer Inst. 92(13) (2000) 1054-1064.

[46] L. Lindh-Astrand, E. Nedstrand, Effects of applied relaxation on vasomotor symptoms in postmenopausal women: a randomized controlled trial, Menopause 20(4) (2013) 401-8.

[47] J. Carpenter, M.L.S. Gass, P.M. Maki, K.M. Newton, J.V. Pinkerton, M. Taylor, W.H. Utian, P.F. Schnatz, A.M. Kaunitz, M. Shapiro, J.L. Shifren, H.N. Hodis, S.A. Kingsberg, J.H. Liu, G. Richard-Davis, N. Santoro, L.L. Sievert, I. Schiff, C. Pike, P. Allen, Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society, Menopause-J. N. Am. Menopause Soc. 22(11) (2015) 1155-1174.

[48] M.S. Hunter, E. Mann, A cognitive model of menopausal hot flushes and night sweats, J Psychosom Res 69(5) (2010) 491-501.

[49] M.S. Hunter, K.L.M. Liao, Evaluation of a four-session cognitive-behavioural intervention for menopausal hot flushes, Br. J. Health Psychol. 1 (1996) 113-125.

[50] J.E. Owen, J.C. Klapow, D.L. Roth, L. Nabell, D.C. Tucker, Improving the effectiveness of adjuvant psychological treatment for women with breast cancer: the feasibility of providing online support, Psychooncology 13(4) (2004) 281-292.

[51] J.C. Mewes, W.H. van Harten, S.F. Duijts, H.S. Oldenburg, M. Van Beurden, M.M. Stuiver, M.S. Hunter, J.M. Kieffer, L.M.G. Steuten, N.K. Aaronson, Cost-effectiveness of cognitive behavioral therapy and physical exercise for alleviating treatment-induced menopausal symptoms in breast cancer patients, 2013.

[52] A. Barak, L. Hen, M. Boniel-Nissim, N. Shapira, A comprehensive review and a meta-analysis of the effectiveness of Internet-based psychotherapeutic interventions., Journal of Technology in Human Services Vol.26(2-4) (2008) 109-160.

[53] V. Spek, P. Cuijpers, I. Nyklicek, H. Riper, J. Keyzer, V. Pop, Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis, Psychol Med 37(3) (2007) 319-28.

[54] G. Andersson, Using the Internet to provide cognitive behaviour therapy, Behav. Res. Ther. 47(3) (2009) 175-180.
[55] Y. Leykin, S.M. Thekdi, D.M. Shumay, R.F. Munoz, M. Riba, L.B. Dunn, Internet interventions for improving psychological well-being in psycho-oncology: review and recommendations, Psycho-Oncol. 21(9) (2012) 1016-1025.
[56] P. Cuijpers, A. van Straten, G. Andersson, Internet-administered cognitive behavior therapy for health problems: A systematic review., J. Behav. Med. Vol.31(2) (2008) 169-177.
[57] A. Barak, L. Hen, M. Boniel-Nissim, N.a. Shapira, A Comprehensive Review and a Meta-Analysis of the Effectiveness of Internet-Based Psychotherapeutic Interventions, Journal of Technology in Human Services 26(2-4) (2008) 109-160.
[58] G. Andersson, P. Cuijpers, P. Carlbring, H. Riper, E. Hedman, Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis, World psychiatry : official journal of the World Psychiatric Association (WPA) 13(3) (2014) 288-95.
[59] H. Christensen, K.M. Griffiths, L. Farrer, Adherence in Internet Interventions for Anxiety and Depression: Systematic Review, Journal of medical Internet research 11(2) (2009) 16.
[60] L. Donkin, H. Christensen, S.L. Naismith, B. Neal, I.B. Hickie, N. Glozier, A systematic review of the impact of adherence on the effectiveness of e-therapies, Journal of medical Internet research 13(3) (2011) e52.
[61] K.M. Melville, L.M. Casey, D.J. Kavanagh, Dropout from Internet-based treatment for psychological disorders, Br. J. Clin. Psychol. 49 (2010) 455-471.
[62] L. Beatty, C. Binnion, A Systematic Review of Predictors of, and Reasons for, Adherence to Online Psychological Interventions, International journal of behavioral medicine (2016).
[63] B. Palmqvist, P. Carlbring, G. Andersson, Internet-delivered treatments with or without therapist input: does the therapist factor have implications for efficacy and cost?, Expert review of pharmacoeconomics & outcomes research 7(3) (2007) 291-7.
[64] G. Clarke, D. Eubanks, E. Reid, C. Kelleher, E. O'Connor, L.L. DeBar, F. Lynch, S. Nunley, C. Gullion, Overcoming depression on the Internet (ODIN) (2): A randomized trial of a self-help depression skills program with reminders, Journal of medical Internet research 7(2) (2005) 11.
[65] G. Alkhaldi, F.L. Hamilton, R. Lau, R. Webster, S. Michie, E. Murray, The Effectiveness of Prompts to Promote Engagement With Digital Interventions: A Systematic Review, Journal of medical Internet research 18(1) (2016) 14.
[66] T. Berger, K. Hammerli, N. Gubser, G. Andersson, F. Caspar, Internet-based treatment of depression: a randomized controlled trial comparing guided with unguided self-help, Cogn Behav Ther 40(4) (2011) 251-66.
[67] T. Berger, F. Caspar, R. Richardson, B. Kneubühler, D. Sutter, G. Andersson, Internet-based treatment of social phobia: A randomized controlled trial comparing unguided with two types of guided self-help, Behav. Res. Ther. 49(3) (2011) 158-169.

[68] S. Norton, J. Chilcot, M.S. Hunter, Cognitive-behavior therapy for menopausal symptoms (hot flushes and night sweats): moderators and mediators of treatment effects, Menopause-J. N. Am. Menopause Soc. 21(6) (2014) 574-578.
[69] M.S. Hunter, K.L.M. Liao, A psychological analysis of menopausal hot flushes, Br. J. Clin. Psychol. 34 (1995) 589-599.
[70] N.W. Scott, G.C. McPherson, C.R. Ramsay, M.K. Campbell, The method of minimization for allocation to clinical trials. a review., Control Clin Trials 23(6) (2002) 662-674.
[71] M.S. Hunter, S. Coventry, H. Hamed, I. Fentiman, E.A. Grunfeld, Evaluation of a group cognitive behavioural intervention for women suffering from menopausal symptoms following breast cancer treatment, Psychooncology 18(5) (2009) 560-3.
[72] L.J. Fallowfield, S.K. Leaity, A. Howell, S. Benson, D. Cella, Assessment of quality of life in women undergoing hormonal therapy for breast cancer: validation of an endocrine symptom subscale for the FACT-B, Breast Cancer Res Treat 55(2) (1999) 189-199.
[73] K. Thirlaway, L. Fallowfield, J. Cuzick, The Sexual Activity Questionnaire: a measure of women's sexual functioning, Qual Life Res 5(1) (1996) 81-90.
[74] A. de Weerd, S. de Haas, A. Otte, D.K. Trenite, G. van Erp, A. Cohen, M. de Kam, J. van Gerven, Subjective sleep disturbance in patients with partial epilepsy: a questionnaire-based study on prevalence and impact on quality of life, Epilepsia 45(11) (2004) 1397-1404.
[75] A.S. Zigmond, R.P. Snaith, The hospital anxiety and depression scale, Acta Psychiatr Scand 67(6) (1983) 361-370.
[76] I. Bjelland, A.A. Dahl, T.T. Haug, D. Neckelmann, The validity of the Hospital Anxiety and Depression Scale - An updated literature review, Journal of Psychosomatic Research 52(2) (2002) 69-77.
[77] C.A. McHorney, J.E. Ware, Jr., J.F. Lu, C.D. Sherbourne, The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups, Med Care 32(1) (1994) 40-66.
[78] N.K. Aaronson, M. Muller, P.D.A. Cohen, M.L. Essink-Bot, M. Fekkes, R. Sanderman, M.A.G. Sprangers, A.T. Velde, E. Verrips, Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations, Journal of Clinical Epidemiology 51(11) (1998) 1055-1068.
[79] M.S. Hunter, J. Chilcot, Testing a cognitive model of menopausal hot flushes and night sweats, Journal of Psychosomatic Research 74(4) (2013) 307-312.
[80] M.J. Rendall, L.M. Simonds, M.S. Hunter, The Hot Flush Beliefs Scale: a tool for assessing thoughts and beliefs associated with the experience of menopausal hot flushes and night sweats, Maturitas 60(2) (2008) 158-169.
[81] M.S. Hunter, B. Ayers, M. Smith, The Hot Flush Behavior Scale: a measure of behavioral reactions to menopausal hot flushes and night sweats, Menopause 18(11) (2011) 1178-1183.

[82] R. Schwarzer, M. Jerusalem, Generalized Self-Efficacy scale in: J. Weinman, S. Wright, M. Johnston (Eds.), Measures in health psychology: A user's portfolio. Causal and control beliefs NFER-Nelson, Windsor, UK, 1995, pp. 35-37.
[83] C.D. Sherbourne, A.L. Stewart, The MOS social support survey, Social science & medicine (1982) 32(6) (1991) 705-14.
[84] I. Ajzen, THE THEORY OF PLANNED BEHAVIOR, Organ. Behav. Hum. Decis. Process. 50(2) (1991) 179-211.
[85] J. Brazier, T. Usherwood, R. Harper, K. Thomas, Deriving a preference-based single index from the UK SF-36 Health Survey, J Clin Epidemiol 51(11) (1998) 1115-1128.
[86] C.v.z. (CVZ), Handleiding voor kostenonderzoek, Methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg, Geactualiseerde versie 2015, 2015.
[87] L.P. Garrison, Jr., E.C. Mansley, T.A. Abbott, 3rd, B.W. Bresnahan, J.W. Hay, J. Smeeding, Good research practices for measuring drug costs in cost-effectiveness analyses: a societal perspective: the ISPOR Drug Cost Task Force report--Part II, Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 13(1) (2010) 8-13.
[88] J. Cohen, Statistical power analysis for the behavioral sciences, Lawrence Earlbaum Associates, Hillsdale, New Jersey, 1988.
[89] P. Diggle, P. Heagerty, K. Liang, S. Zeger, Analysis of longitudinal data., Oxford University Press, New York, 2002.
[90] G.R. Norman, J.A. Sloan, K.W. Wyrwich, Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation, Med Care 41(5) (2003) 582-592.
[91] M.C. Weinstein, Recent developments in decision-analytic modelling for economic evaluation, PharmacoEconomics 24(11) (2006) 1043-53.
[92] E. Fenwick, K. Claxton, M. Sculpher, Representing uncertainty: the role of cost-effectiveness acceptability curves, Health economics 10(8) (2001) 779-87.
[93] A. Briggs, M. Sculpher, K. Claxton, Decision Modelling for Health Economic Evaluation, Oxford University Press Oxford, 2006.
[94] Uniform Requirements for Manuscripts Submitted to Biomedical Journals, New England Journal of Medicine 336(4) (1997) 309-316.

CHAPTER 4

# EFFICACY OF INTERNET-BASED COGNITIVE BEHAVIORAL THERAPY FOR TREATMENT-INDUCED MENOPAUSAL SYMPTOMS IN BREAST CANCER SURVIVORS: RESULTS OF A RANDOMIZED CONTROLLED TRIAL



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# ABSTRACT

## Purpose

We evaluated the effect of Internet-based cognitive behavioral therapy (iCBT), with or without therapist support, on the perceived impact of hot flushes and night sweats (HF/NS) and overall levels of menopausal symptoms (primary outcomes), and sleep quality, HF/NS frequency, sexual functioning, psychological distress and health-related quality of life in breast cancer (BC) survivors with treatment-induced menopausal symptoms.

## Methods

We randomly assigned 254 BC survivors to a therapist guided or a self-managed iCBT group or to a waiting list control group. The six-week iCBT program included psycho-education, behavioral monitoring and cognitive restructuring. Questionnaires were administered at baseline (T0), and at 10 weeks (T1) and 24 weeks (T2) post-randomization. We used mixed-effects models to compare the intervention groups with the control group over time. P-value was set at $p < .01$. An effect size (ES) of .20 was considered small, .50 moderate and clinically significant and .80 large.

## Results

Compared with the control group, the guided and self-managed iCBT groups reported a significant decrease in the perceived impact of HF/NS ($p < .001$; ES = .63 and $p < .001$; ES = .56) and improvement in sleep quality ($p < .001$; ES = .57 and $p = .001$; ES = .41). The guided group also reported significant improvement in overall levels of menopausal symptoms ($p = .003$; ES = .33), and night sweats frequency ($p < .001$; ES = .64). At longer-term follow-up (T2), the effects remained significant, with smaller ES, for the guided group on perceived impact of HF/NS and sleep quality, and for the self-managed group on overall levels of menopausal symptoms. Additional longer-term effects for both intervention groups were found on hot flush frequency.

## Conclusion

Internet-based CBT, with or without therapist support, has clinically significant, salutary effects on the perceived impact and frequency of HF/NS, overall levels of menopausal symptoms and sleep quality.

## INTRODUCTION

Adjuvant treatment of breast cancer (BC), including chemotherapy, oophorectomy and/or endocrine therapy, can lead to treatment-induced menopausal symptoms in (young) BC survivors [1-6] Hot flushes and night sweats (HF/NS) are the most prevalent (63% to 85%) and disruptive menopausal symptoms[7-13]. Menopausal symptoms not only affect women's daily functioning and health-related quality of life (HRQOL) [4, 8, 9, 14, 15], but also can result in under-compliance or discontinuation of endocrine treatment [16, 17].

Medical treatment of menopausal symptoms, including gabapentin, clonidine and selective serotonin reuptake inhibitors are moderately effective, but can have bothersome adverse effects [18-22]. In addition, many BC survivors prefer a nonmedical approach [7]. Hunter and colleagues developed a cognitive behavioral therapy (CBT) program to help women to cope with their HF/NS [23-26]. Three randomized controlled trials (RCTs) have demonstrated the efficacy of a group-based version of this CBT program in decreasing the perceived impact of HF/NS in healthy women and BC survivors [27-29]. Positive effects also were observed for a self-help version with minimal support (by telephone or face-to-face) in women with naturally occurring menopause [27, 30]. However, practical issues, including scheduling conflicts and travel distance, may represent significant barriers to the successful implementation of (group-based) face-to-face CBT programs. Duijts et al. [29] reported that more than 50% of BC survivors in a Dutch trial attended less than two-thirds of the planned group CBT sessions.

Internet-based CBT presents a more contemporary and flexible alternative to face-to-face sessions, and may result in higher participation rates and better compliance. Women who participated in the Duijts et al. [29] trial expressed interest in and willingness to participate in such a program [29]. Several studies have reported positive effects of guided iCBT on a range of psychosocial problems in the general population and in cancer survivors [31-36]. Guided iCBT has been reported to be as effective as face-to-face CBT [31, 37-39]. Internet-based interventions without therapist support often have been associated with lower compliance rates and smaller effects than guided interventions [32, 40, 41]. However, because of their potential for further increasing reach and decreasing costs, studies have been conducted to identify ways (e.g., use of reminders) to improve

compliance with and, thus, the efficacy of self-managed Internet-based interventions [31, 42-44].

We conducted a pilot study to develop, evaluate the feasibility of, and generate initial data on the potential efficacy of a guided iCBT program, that is based on the model of Hunter and colleagues, [23-26] for alleviating menopausal symptoms in BC survivors [45]. The positive results of that study led to the current RCT to evaluate the efficacy of an iCBT program, with or without therapist support, in women with BC treatment-induced menopausal symptoms. We hypothesized that women allocated to the iCBT groups would report a greater decrease in the perceived impact of HF/NS and overall levels of menopausal symptoms than women in the waiting list control group. Secondarily, we hypothesized that women allocated to the iCBT groups would report a greater improvement in sleep quality, HF/NS frequency, sexual functioning, psychological distress and HRQOL. No direct comparison was planned between the two intervention groups.

## METHODS

### Research Design and Study Sample

A detailed description of the RCT has been reported elsewhere [46]. Briefly, women were eligible if they had histologically confirmed BC, were 50 years of age at the time of diagnosis, had undergone chemotherapy and/or an oophorectomy (completed at a minimum of 4 months and a maximum of 5 years before study entry, with the exception of trastuzumab use) and/or endocrine treatment (including ongoing use), were disease-free at time of study entry, and had experienced treatment-induced problematic HF/NS (as indicated by an average score of ≥2 on the problem-rating subscale of the Hot Flush Rating Scale [HFRS]; Data Supplement [47]) for at least 2 months, with a minimum of 10 HF/NS in the past week. Women were excluded if they had a prior diagnosis of another type of cancer (except basal cell carcinoma), had serious overt cognitive or psychiatric comorbidity, did not speak Dutch, had no Internet access or were participating in concurrent studies/rehabilitation programs aimed at alleviating or coping with menopausal symptoms. Patients were recruited from 12 community and academic hospitals in the Netherlands. The study was approved by the Institutional Review Boards of all hospitals.

## Procedure and Timing of Assessments

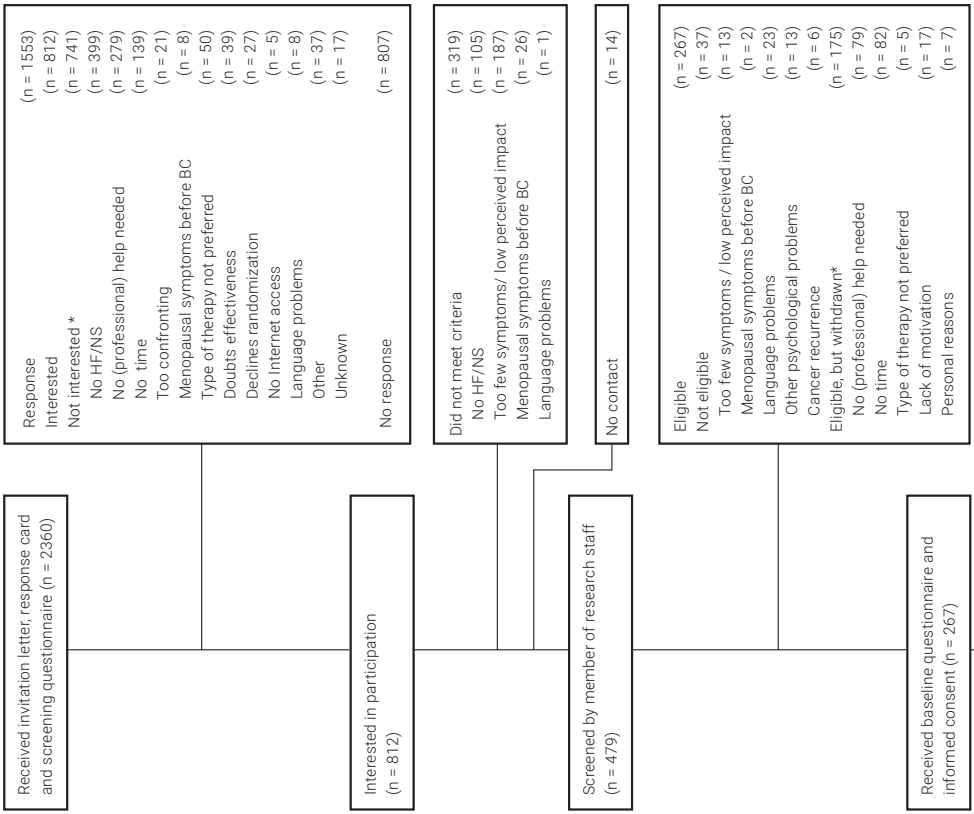
Potentially eligible patients were identified through hospital registries or the Netherlands Cancer Registry. Invitations were sent by the treating physicians with an information brochure, a screening questionnaire that assessed menopausal status before and after cancer treatment, type and timing of cancer treatment, the presence of problematic HF/NS, and a response card to indicate, if relevant, reasons for non-participation. Subsequently, a member of the research staff screened interested and potentially eligible patients by telephone to confirm the presence and nature of their HF/NS, their willingness to invest time in the iCBT and final eligibility (Figure 1).

Upon return of informed consent and the online baseline questionnaire, participants were randomly assigned to the guided or self-managed intervention group or a waiting list control group (ratio 1:1:1). Minimization techniques [48] were applied using a randomization program (ALEA, FormVision, Abcoude, the Netherlands) to create balanced groups with respect to age, time since chemotherapy, current endocrine treatment, and current use of prescription drugs for HF/NS. Online follow-up assessments were administered at 10 weeks (T1) and 24 weeks (T2) postrandomization.



## Intervention Groups

Participants in the two intervention groups were given access to the same 6-week iCBT program. The focus of the program was on HF/NS, but other topics, including stress management and sleep problems also were addressed. The program consisted of 6 modules, each including elements of self-reflection, psycho-education and assignments (both in-module and as homework; Table 1). The participants also had access to a diary application to register their HF/NS. Information was provided through written texts and video clips presented by experts and BC survivors with similar menopausal symptoms. The average estimated time per week to complete a module was 1 hour, with an additional 30 minutes per day to carry out the relaxation and homework assignments. Weekly reminders were sent to promote continued use of the iCBT program.


Received invitation letter, response card and screening questionnaire (n = 2360)
Response (n = 1553)
Interested (n = 812)
Not interested * (n = 741)
No HF/NS (n = 399)
No (professional) help needed (n = 279)
No time (n = 139)
Too confronting (n = 21)
Menopausal symptoms before BC (n = 8)
Type of therapy not preferred (n = 50)
Doubts effectiveness (n = 39)
Declines randomization (n = 27)
No Internet access (n = 5)
Language problems (n = 8)
Other (n = 37)
Unknown (n = 17)
No response (n = 807)
Interested in participation (n = 812)
Did not meet criteria (n = 319)
No HF/NS (n = 105)
Too few symptoms/ low perceived impact (n = 187)
Menopausal symptoms before BC (n = 26)
Language problems (n = 1)
No contact (n = 14)
Screened by member of research staff (n = 479)
Eligible (n = 267)
Not eligible (n = 37)
Too few symptoms / low perceived impact (n = 13)
Menopausal symptoms before BC (n = 2)
Language problems (n = 23)
Other psychological problems (n = 13)
Cancer recurrence (n = 6)
Eligible, but withdrawn* (n = 175)
No (professional) help needed (n = 79)
No time (n = 82)
Type of therapy not preferred (n = 5)
Lack of motivation (n = 17)
Personal reasons (n = 7)
Received baseline questionnaire and informed consent (n = 267)

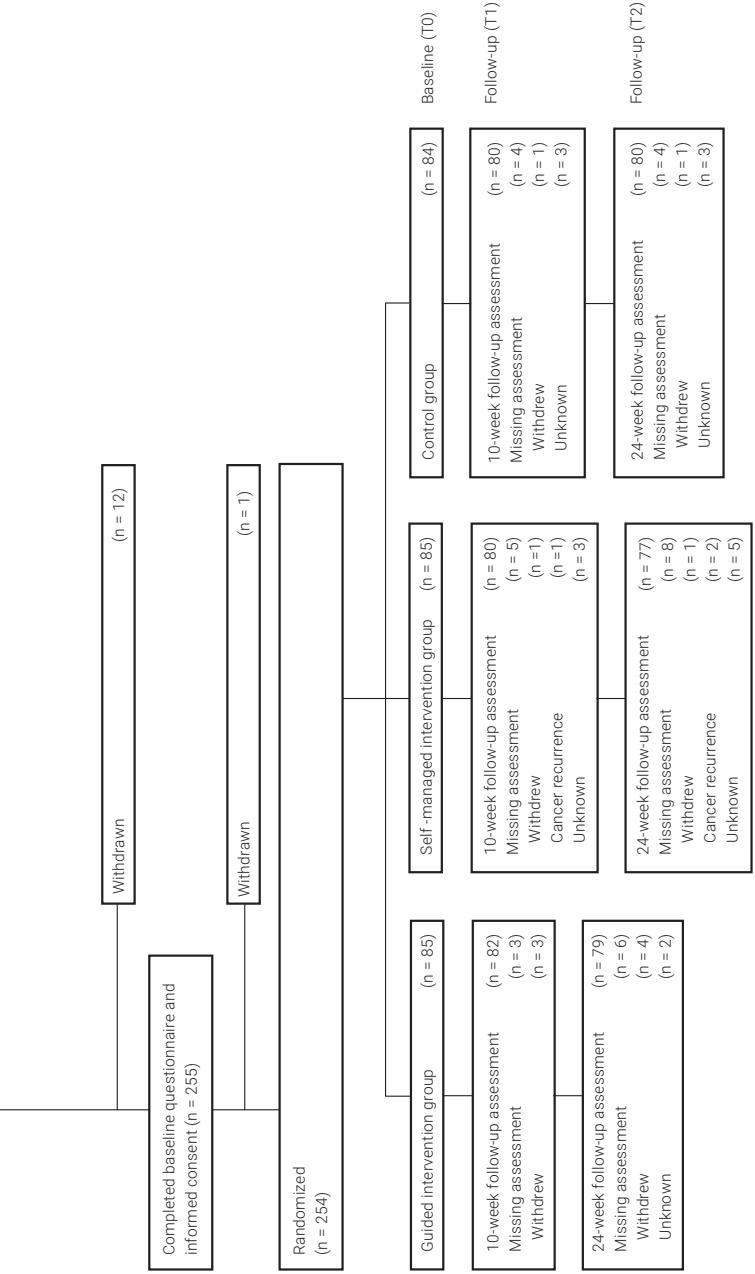



**Figure 1.** CONSORT diagram.
Abbreviations: HF/NS, hot flushes / night sweats; T0, baseline assessment; T1, 10-week follow-up assessment; T2, 24-week follow-up assessment.
* Patients could provide more than 1 reason.

Participants in the guided group received a telephone interview before the start of the online program and weekly written feedback throughout the 6-week period. This feedback was provided by trained medical social workers and psychologists with access to the online entries of the women. If required, additional contact could take place through a built-in e-mail application. Fidelity checks and supervisory meetings were held throughout the RCT.

### Waiting list Control Group

Participants randomly assigned to the waiting list control group received usual care, which did not include any specific programs or clinical pathways for dealing with menopausal symptoms. They were offered the opportunity to follow the iCBT program upon completion of the last follow-up assessment.

### Study Measures

Sociodemographic and clinical information was obtained through the screening process and the baseline questionnaire. Standardized self-report questionnaires were administered to assess the primary and secondary outcomes (Appendix Table A1). Primary outcomes included the perceived impact of HF/NS (the problem rating subscale of the HFRS [47]), and overall levels of menopausal symptoms (the Functional Assessment of Cancer Treatment- Endocrine Symptoms; FACT-ES [49]).

Secondary outcomes included sleep quality (Groningen Sleep Quality Scale; GSQS [50, 51]), frequency of HF/NS (HFRS frequency subscale [47]), sexual functioning (Sexual Activity Questionnaire; SAQ [52]), psychological distress (Hospital Anxiety and Depression Scale; HADS [53, 54]) and HRQOL (36-item Short Form Health Survey; SF-36 [55, 56]). A slightly modified scoring procedure was used for the SAQ to enable sexually inactive women to complete the questionnaire.

Compliance rates were calculated on the basis of log data. A module was considered completed when the participant closed the session to proceed to the next module. Completion of at least the first three modules was considered an acceptable (minimal) compliance level because these modules cover the core issues of the program.

**Table 1.** Description of and access to the Internet-Based CBT

| |
|---|
| **Module 1: Welcome**<br>• Introduction to the online program<br>• Psycho-education about the effect of breast cancer on menopause, menopausal symptoms and the positive influence of relaxation techniques<br>• In-session assignments: making a schedule for reading the sessions and carrying out homework<br>• Homework: keeping a HF/NS diary and practicing relaxation techniques |
| **Module 2: Hot flushes**<br>• Psycho-education about the physiology of HF/NS and the role and interplay of physical symptoms, thoughts, feelings and behaviors<br>• In-session assignments: recognizing patterns of and triggers for hot flushes and cognitive restructuring of unhelpful thoughts<br>• Homework: as before plus monitoring triggers and applying helpful thoughts |
| **Module 3: From stressing to relaxing**<br>• Psycho-education about stress, the relationship between stress and hot flushes, and cognitive and behavioral stress management techniques<br>• In-session assignments: identification of stressful events and usual reactions to stress and goal setting to reduce stress<br>• Homework: as before plus pursuing self-formulated goals to reduce stress |
| **Module 4: Improving sleep**<br>• Psycho-education about the influence of night sweats on sleep quality and sleep problems and helpful cognitive and behavioral reactions to night sweats/sleep problems<br>• In-session assignments: sleep hygiene questionnaire and goal setting to improve sleep quality<br>• Homework: as before plus pursuing self-formulated goals to improve the quality of sleep |
| **Module 5: My body and sexuality**<br>• Psycho-education about sexual problems and weight gain, cognitive and behavioral precipitants and consequences of sexual problems and weight gain<br>• In-session assignments: goal setting to reduce sexual problems (if present) and weight (if present)<br>• Homework: as before plus pursuing self-formulated goals (if specified) to reduce sexual problems and/or weight |
| **Module 6: Keep progressing**<br>• Psycho-education about the benefits of using an action plan<br>• In-session assignments: identification of helpful cognitive and/or behavioral techniques as discussed/learned throughout each module, goal setting to implement the maintenance plan and identification of possible barriers and actions to overcome them<br>• Homework: as before plus implementing the maintenance plan |
| **Access to and completion of the modules**<br>• Self-management group: access to the entire iCBT program in fixed order from time of enrollment forward, but were advised and encouraged to follow the program using a weekly schedule for 6 consecutive weeks. The average time to complete the six modules was 5.7 weeks (SD = 2.23).<br>• Guided group: access to the entire iCBT program in fixed order, access to the next module after weekly feedback of the therapist. The average time to complete the six modules was 6.6 weeks (SD = 1.25). |

Abbreviations: CBT, cognitive behavioral therapy; HF/NS, hot flushes / night sweats.

### Statistical Analyses

With more than 64 participants per study arm, the study had 80% power to detect an effect size (ES) of .50 with a two-tailed p-value set at .05 [57]. The $X^2$ test and univariable analysis of variance were used to compare the baseline characteristics of the three groups. Scores on the outcomes were calculated according to published algorithms. If a participant completed at least one half of the items from a subscale, missing items were replaced by the average score of the completed items in that same scale.

To model between-group differences in change from baseline to follow-up, we used mixed-effects models with a random intercept, an autoregressive covariance structure, and a restricted maximum likelihood solution, with the control group as reference group [58]. The p-value of the omnibus test for overall group-by-time interaction was set at .05. If significant, we then evaluated specific contrasts (i.e. differences between the control group and the two intervention groups in mean change from T0 to T1 and from T0 to T2). We used a p-value of .01 for the specific contrasts to minimize the risk of type I errors as a result of multiple testing. Group differences over time in mean change scores were accompanied by Cohen's ES. An ES of .20 was considered small, .50 moderate and clinically significant and .80 large [57, 59].

At the individual patient level, we determined clinically significant improvement for each participant on the basis of a 2-point change (1 standard deviation [SD]) on the problem rating subscale of the HFRS [27, 28] and a 0.5 SD improvement on the FACT-ES [49, 59, 60]. Bonferroni-corrected $X^2$ tests were used to compare the percentages of women with clinically significant improvement on the HFRS and FACT-ES between groups. All analyses were conducted on an intention-to-treat basis.

## RESULTS

Patient recruitment took place between September 2015 and March 2017. Initial invitations were sent to 2,360 women who met the most basic eligibility criteria. Thirty-four percent did not respond, and 31.4% indicated that they had no interest in participating in the trial. Reasons for nonparticipation are shown in the CONSORT diagram (Figure 1).

Of the 812 potentially interested women, 319 did not meet the screening criteria primarily because of the frequency and perceived impact of their

HF/NS. Of the remaining 493 women, 479 were interviewed by telephone to establish final eligibility, and 14 were unreachable. Thirty-seven women were excluded and 175 women ultimately declined participation. Two-hundred and fifty-four of the remaining 267 women provided written informed consent, completed the baseline questionnaire, and were randomly assigned to the guided intervention group (n = 85), the self-managed intervention group (n = 85), or the control group (n = 84). Completion rates of follow-up assessments T1 (n = 242; 95.3%) and T2 (n = 236; 92.9%) did not differ significantly among groups.

The mean age of the study sample was 47.4 years (SD = 5.45 years). The majority of participants were in a relationship (85.8%) and employed (78%). The average time since diagnosis was 3.1 years (SD = 1.32 years). All participants had undergone surgery and most had received radiotherapy (77.6%), chemotherapy (93.3%), and/or endocrine treatment (85.4%). At the time of study entry, 80.7% of the participants were still undergoing endocrine treatment. Fifty-six percent reported having experienced HF/NS for a period of 1 to 3 years, and 10.2% indicated that they used prescription drugs for their HF/NS. All baseline sociodemographic and clinical characteristics were balanced across groups, except surgery type (breast conserving versus mastectomy), which was associated only with the social functioning subscale of the SF-36, and was adjusted for in the analyses of that subscale (Tables 2 and 3).

All six modules of the iCBT program were completed by 85.9% and 62.4% of participants in the guided and the self-managed intervention groups, respectively. With the minimal compliance rate set at the completion of three modules, these percentages were 90.6% for the guided and 78.8% for the self-managed intervention groups. Time constraints were the most commonly cited reason for low compliance.

## Primary Outcomes

Results of the intention-to-treat analyses indicated a significant overall group-by-time interaction for the perceived impact of HF/NS (HFRS problem rating subscale, $p < .001$) and overall levels of menopausal symptoms (FACT-ES, $p = .01$). Subsequently, the specific contrasts showed that compared to the control group, both the guided and self-managed iCBT groups reported a clinically and statistically significant short-term decrease in the perceived impact of HF/NS (ES = .63 and .56, respectively; both $p < .001$). The guided group also reported a statistically significant, longer-term decrease in the

**Table 2.** Sociodemographic, Clinical and HF/NS Characteristics

| | No. (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **All Patients (n= 254)** | | **Guided Intervention (n= 85)** | | **Self-managed Intervention (n= 85)** | | **Control (n= 84)** | |
| **Patient Characteristics** | | | | | | | | |
| Age, years | | | | | | | | |
| Mean | 47.4 | | 47.5 | | 47.7 | | 47.0 | |
| SD | 5.45 | | 5.14 | | 5.73 | | 5.50 | |
| Education | | | | | | | | |
| Primary education | 2 | (0.8) | 0 | (0.0) | 2 | (2.4) | 0 | (0.0) |
| High school & vocational education | 136 | (53.5) | 48 | (56.5) | 41 | (48.2) | 47 | (56.0) |
| College/university | 116 | (45.7) | 37 | (43.5) | 42 | (49.4) | 37 | (44.0) |
| Married or in a relationship | 217 | (85.8) | 74 | (88.1) | 71 | (83.5) | 72 | (85.7) |
| Part- or full-time job | 198 | (78.0) | 67 | (78.8) | 62 | (72.9) | 69 | (82.1) |
| BMI | | | | | | | | |
| Mean | 26.12 | | 26.41 | | 26.22 | | 25.73 | |
| SD | 4.71 | | 5.48 | | 4.41 | | 4.16 | |
| Comorbid health conditions | | | | | | | | |
| none | 143 | (56.3) | 48 | (56.5) | 51 | (60.0) | 44 | (52.4) |
| 1 | 71 | (28.0) | 24 | (28.2) | 21 | (24.7) | 26 | (31.0) |
| ≥ 2 | 40 | (15.7) | 13 | (15.3) | 13 | (15.3) | 14 | (16.7) |
| **Treatment characteristics** | | | | | | | | |
| Time since diagnosis, years | | | | | | | | |
| Mean | 3.1 | | 3.2 | | 3.0 | | 3.0 | |
| SD | 1.32 | | 1.33 | | 1.29 | | 1.33 | |
| <1 year | 3 | (1.2) | 0 | (0.0) | 2 | (2.4) | 1 | (1.2) |
| 1 - 2 years | 129 | (50.8) | 38 | (44.7) | 48 | (56.5) | 43 | (51.2) |
| 3 - 5 years | 92 | (36.2) | 35 | (41.2) | 27 | (31.8) | 30 | (35.7) |
| > 5 years | 30 | (11.8) | 12 | (14.1) | 8 | (9.4) | 10 | (11.9) |

(continued on following page)

**Table 2.** Sociodemographic, Clinical and HF/NS Characteristics (continued)

| | No. (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **All Patients (n= 254)** | | **Guided Intervention (n= 85)** | | **Self-managed Intervention (n= 85)** | | **Control (n= 84)** | |
| Surgery | 254 | (100) | | | | | | |
| Breast conserving treatment* | 109 | (42.9) | 27 | (31.8) | 38 | (44.7) | 44 | (52.4) |
| Mastectomy | 145 | (57.1) | 58 | (68.2) | 47 | (55.3) | 40 | (47.6) |
| Radiotherapy | 197 | (77.6) | 60 | (70.6) | 69 | (81.2) | 68 | (81.0) |
| Chemotherapy | 237 | (93.3) | 82 | (96.5) | 77 | (90.6) | 78 | (92.9) |
| Immunotherapy (prior and current) | 61 | (24.0) | 28 | (32.9) | 16 | (18.8) | 17 | (20.2) |
| Current use | 7 | (2.8) | 3 | (3.5) | 3 | (3.5) | 1 | (1.2) |
| Endocrine therapy (prior and current) | 217 | (85.4) | 71 | (83.5) | 72 | (84.7) | 74 | (88.1) |
| Current use | 205 | (80.7) | 69 | (81.2) | 68 | (80.0) | 68 | (81.0) |
| Oophorectomy | 47 | (18.5) | 17 | (20.0) | 14 | (16.5) | 16 | (19.0) |
| **HF/NS characteristics** | | | | | | | | |
| Duration of HF/NS | | | | | | | | |
| 2 - 6 months | 16 | (6.3) | 4 | (4.7) | 4 | (4.7) | 8 | (9.5) |
| 7 - 12 months | 38 | (15.0) | 15 | (17.6) | 15 | (17.6) | 8 | (9.5) |
| 1 - 3 years | 142 | (55.9) | 46 | (54.1) | 45 | (52.9) | 51 | (60.7) |
| > 3 years | 58 | (22.8) | 20 | (23.5) | 21 | (24.7) | 17 | (20.2) |
| Prescribed medication for HF/NS at baseline** | 26 | (10.2) | 6 | (7.1) | 9 | (10.6) | 11 | (13.1) |
| Prescribed medication for HF/NS during the trial | 19 | (8.1) | 4 | (5.0) | 5 | (5.4) | 10 | (12.7) |
| Other remedies used to reduce HF/NS during the trial *** | | | | | | | | |
| Herbal preparations | 14 | (6.5) | 8 | (10.1) | 6 | (8.1) | 0 | (0) |
| Yoga | 29 | (12.5) | 9 | (11.4) | 10 | 13.5) | 10 | (12.7) |
| Acupuncture | 7 | (3.0) | 2 | (2.5) | 2 | (2.7) | 3 | (3.8) |

Abbreviations: No., number; HF/NS, hot flushes / night sweats; SD, standard deviation. * P= .024 for surgery type. There were no statistically significant differences between groups at baseline on any other variables.

** Prescribed medication include anti-depressants, clonidine, gabapentin and stellate ganglion block.

*** Categories are not exclusive (n=232).

perceived impact of HF/NS (ES 48; $p = .002$). We also observed a significant short-term improvement for the guided group (ES = .33; $p = .003$) and a significant longer-term improvement for the self-managed group (ES = .34; $p = .006$;) in overall levels of menopausal symptoms, compared to the control group (Figure 2).

At the individual patient level, 42.7% of the participants in the guided group and 35% in the self-managed group showed a short-term, clinically significant improvement (at least a 2-point change) in perceived impact of HF/NS compared with 17.5% of the women in the control group ($p < .05$ for both). We observed longer-term, clinically significant improvement in the perceived impact of HF/NS in 45.6% of participants in the guided group and 39.0% in the self-managed group compared with 26.3% in the control group (guided vs control $p < .05$).

For overall levels of menopausal symptoms, the percentages of short-term clinically significant improvement were 44.4% in the guided group and 31.3% in the self-managed group compared with 22.5% in the control group (guided *v* control $p < .05$). In the longer-term, 43.6% of women in the guided group, 39.0% in the self-managed group, and 22.5% in the control group reported a clinically significant improvement in overall levels of menopausal symptoms (guided *v* control $p < .05$).

## Secondary Outcomes

A significant overall group-by-time interaction was observed for sleep quality (Groningen Sleep Quality Scale, $p < .001$), hot flush frequency (HFRS, frequency subscale, $p = .019$) and night sweats frequency (HFRS, frequency subscale, $p = .006$). The specific contrasts indicated that compared with the control group, the guided group had a clinically and statistically significant short-term improvement (ES = .57; $p < .001$) and a significant longer-term improvement in sleep quality (ES = .47; $p < .001$). For the self-managed group, we also observed a significant short-term improvement (ES = .41; $p = .001$) in sleep quality.

In addition, both the guided and self-managed groups reported a statistically significant longer-term decrease in frequency of hot flushes (ES = .48 for both; $p = .005$ and .006, respectively), and the guided group showed a clinically and statistically significant short-term decrease in night sweats (ES = .64; $p < .001$), compared with the control group. No significant overall group-by-time interactions were observed for any of the scales that assessed sexual functioning (SAQ), psychological distress (HADS), or HRQOL (SF-36).

## DISCUSSION

The results of this RCT support our hypothesis that iCBT, with or without therapist support, has a positive effect on the perceived impact of HF/NS and overall levels of menopausal symptoms. We also found a positive effect on sleep quality and frequency of HF/NS. As expected, estimates of clinically significant improvement (ES ≥ .50) favored the guided over the self-managed group.

As hypothesized, our compliance rates were higher than those reported in the Dutch trial that evaluated the efficacy of group-based CBT in BC survivors with treatment-induced menopausal symptoms [29]. The compliance rates of the guided intervention group (86%) were comparable to those reported in both iCBT and face-to-face CBT programs for the treatment of psychosocial problems [37, 61]. Although lower compliance rates were observed for the completion of all six modules in the self-managed group, a large proportion of women completed the first three modules (79%), which reflected the a-priori formulated minimally acceptable level of compliance.

Our efficacy results are similar to those of three previous RCTs in which a face-to-face CBT program, delivered in group format or as guided self-help, was found superior to a control group in reducing the perceived impact of HF/NS in healthy women and BC survivors [27-29]. We therefore expect that with some modification, the iCBT program could be useful to a broader population of women with menopausal symptoms.

The observed strength of our effects and the percentage of women with a clinically significant improvement in symptoms over time were lower than in two United Kingdom-based trials [27, 28]. Those trials included women who had experienced either natural or BC treatment-induced menopausal symptoms, whereas in our trial, participation was limited to women whose menopausal symptoms were treatment-induced. We suspect that the symptoms experienced by women whose menopausal symptoms were originally treatment-induced may be more resistant to change than is the case with natural menopause [62].

**Table 3.** Between group difference in mean change from baseline to follow-up

| | T0 | | | T1 | | | T2 | | | Between group difference T0-T1 | | | | Between group difference T0-T2 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD | N | Mean | SD | Mean change | SE | p | ES † | Mean change | SE | p | ES † |
| **PRIMARY OUTCOMES** | | | | | | | | | | | | | | | | | |
| **Perceived impact of HF/NS** | | | | | | | | | | | | | | | | | |
| HFRS problem rating (**p < .001#**) | | | | | | | | | | | | | | | | | |
| Guided intervention | 85 | 4.98 | 1.88 | 82 | 3.27 | 1.86 | 79 | 3.34 | 1.85 | -1.19 | 0.25 | **< .001** | .63 | -0.90 | 0.29 | **.002** | .48 |
| Self-managed intervention | 85 | 4.89 | 1.88 | 80 | 3.33 | 1.85 | 77 | 3.41 | 1.85 | -1.04 | 0.25 | **< .001** | .56 | -0.74 | 0.29 | .011 | .40 |
| Control ‡ | 84 | 4.70 | 1.88 | 80 | 4.18 | 1.86 | 80 | 3.96 | 1.86 | | | | | | | | |
| **Overall levels of menopausal symptoms** | | | | | | | | | | | | | | | | | |
| FACT-ES (**p = .01#**) | | | | | | | | | | | | | | | | | |
| Guided intervention | 84 | 50.23 | 8.72 | 82 | 53.88 | 8.67 | 79 | 53.02 | 8.58 | 2.85 | 0.95 | **.003** | .33 | 2.40 | 1.08 | .028 | .27 |
| Self-managed intervention | 85 | 51.22 | 8.75 | 80 | 53.81 | 8.61 | 77 | 54.61 | 8.53 | 1.79 | 0.96 | .062 | .20 | 3.01 | 1.09 | **.006** | .34 |
| Control ‡ | 84 | 50.01 | 8.75 | 80 | 50.82 | 8.63 | 80 | 50.40 | 8.65 | | | | | | | | |
| **SECONDARY OUTCOMES** | | | | | | | | | | | | | | | | | |
| **Sleep quality** | | | | | | | | | | | | | | | | | |
| GSQS (**p < .001#**) | | | | | | | | | | | | | | | | | |
| Guided intervention | 85 | 8.45 | 3.86 | 81 | 6.15 | 3.82 | 79 | 6.30 | 3.80 | -2.21 | 0.47 | **< .001** | .57 | -1.81 | 0.50 | **<.001** | .47 |
| Self-managed intervention | 84 | 8.56 | 3.85 | 79 | 6.89 | 3.79 | 75 | 6.98 | 3.75 | -1.58 | 0.47 | **.001** | .41 | -1.25 | 0.51 | .015 | .32 |
| Control ‡ | 84 | 8.49 | 3.86 | 80 | 8.40 | 3.82 | 79 | 8.15 | 3.81 | | | | | | | | |
| **Hot flush frequency** | | | | | | | | | | | | | | | | | |
| HFRS hot flush frequency (**p = .019#**) | | | | | | | | | | | | | | | | | |
| Guided intervention | 85 | 55.22 | 39.58 | 81 | 39.44 | 39.24 | 78 | 40.35 | 39.14 | -13.37 | 5.70 | .019 | .34 | -18.91 | 6.76 | **.005** | .48 |
| Self-managed intervention | 85 | 48.79 | 39.58 | 79 | 38.76 | 39.08 | 76 | 34.03 | 39.05 | -7.63 | 5.72 | .183 | .19 | -18.81 | 6.79 | **.006** | .48 |
| Control ‡ | 84 | 48.50 | 39.58 | 80 | 46.10 | 39.23 | 80 | 52.54 | 39.38 | | | | | | | | |

(continued on following page)

**Table 3.** Between group difference in mean change from baseline to follow-up (continued)

| | T0 | | | T1 | | | T2 | | | Between group difference T0-T1 | | | | Between group difference T0-T2 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD | N | Mean | SD | Mean change | SE | p | ES † | Mean change | SE | p | ES † |
| **Night sweats frequency** | | | | | | | | | | | | | | | | | |
| HFRS night sweats frequency (**p = .006**#) | | | | | | | | | | | | | | | | | |
| Guided intervention | 84 | 18.29 | 13.21 | 80 | 10.34 | 13.16 | 79 | 11.46 | 13.14 | -8.45 | 2.35 | < .001 | .64 | -5.64 | 2.33 | .016 | .43 |
| Self-managed intervention | 84 | 18.17 | 13.19 | 80 | 14.28 | 13.16 | 76 | 12.07 | 13.09 | -4.39 | 2.36 | .063 | .33 | -4.91 | 2.35 | .038 | .37 |
| Control ‡ | 84 | 18.75 | 13.21 | 79 | 19.25 | 13.15 | 80 | 17.56 | 13.16 | | | | | | | | |
| **Sexual pleasure** | | | | | | | | | | | | | | | | | |
| SAQ pleasure (p = .063#) | | | | | | | | | | | | | | | | | |
| Guided intervention | 85 | 7.03 | 4.63 | 81 | 7.61 | 4.56 | 79 | 7.58 | 4.53 | 0.47 | 0.47 | .322 | .10 | 0.93 | 0.53 | .082 | .20 |
| Self-managed intervention | 85 | 6.07 | 4.63 | 78 | 6.46 | 4.51 | 75 | 7.14 | 4.47 | 0.27 | 0.48 | .565 | .06 | 1.44 | 0.54 | .008 | .31 |
| Control ‡ | 84 | 7.32 | 4.63 | 80 | 7.44 | 4.56 | 79 | 6.95 | 4.55 | | | | | | | | |
| **Discomfort during sex** | | | | | | | | | | | | | | | | | |
| SAQ discomfort § (p = .337#) | | | | | | | | | | | | | | | | | |
| Guided intervention | 62 | 2.34 | 1.76 | 62 | 2.19 | 1.75 | 61 | 2.05 | 1.75 | -0.23 | 0.22 | .285 | .13 | -0.41 | 0.25 | .100 | .24 |
| Self-managed intervention | 64 | 2.17 | 1.79 | 58 | 1.90 | 1.72 | 57 | 1.83 | 1.73 | -0.35 | 0.22 | .112 | .20 | -0.46 | 0.25 | .069 | .26 |
| Control ‡ | 64 | 2.11 | 1.75 | 59 | 2.19 | 1.70 | 56 | 2.23 | 1.69 | | | | | | | | |
| **Intercourse frequency** | | | | | | | | | | | | | | | | | |
| SAQ habit (p = .427#) | | | | | | | | | | | | | | | | | |
| Guided intervention | 83 | 0.53 | 0.71 | 81 | 0.49 | 0.71 | 79 | 0.50 | 0.71 | -0.09 | 0.14 | .535 | .12 | 0.10 | 0.14 | .445 | .15 |
| Self-managed intervention | 85 | 0.46 | 0.71 | 78 | 0.49 | 0.71 | 75 | 0.54 | 0.71 | -0.01 | 0.14 | .928 | .02 | 0.21 | 0.14 | .121 | .30 |
| Control ‡ | 84 | 0.55 | 0.71 | 80 | 0.59 | 0.71 | 79 | 0.41 | 0.71 | | | | | | | | |

(continued on following page)

**Table 3.** Between group difference in mean change from baseline to follow-up (continued)

| | T0 | | | T1 | | | T2 | | | Between group difference T0-T1 | | | | Between group difference T0-T2 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD | N | Mean | SD | Mean change | SE | p | ES † | Mean change | SE | p | ES † |
| **Anxiety** | | | | | | | | | | | | | | | | | |
| HADS anxiety (p = .524#) | | | | | | | | | | | | | | | | | |
| Guided intervention | 85 | 7.06 | 4.01 | 81 | 5.76 | 3.95 | 79 | 6.53 | 3.92 | -0.68 | 0.44 | .122 | .17 | -0.21 | 0.46 | .648 | .05 |
| Self-managed intervention | 85 | 6.36 | 4.01 | 78 | 5.38 | 3.91 | 76 | 5.64 | 3.88 | -0.37 | 0.44 | .411 | .09 | -0.40 | 0.47 | .393 | .10 |
| Control ‡ | 84 | 6.85 | 4.01 | 80 | 6.24 | 3.95 | 79 | 6.53 | 3.94 | | | | | | | | |
| **Depression** | | | | | | | | | | | | | | | | | |
| HADS depression (p = .353#) | | | | | | | | | | | | | | | | | |
| Guided intervention | 85 | 4.79 | 3.54 | 81 | 3.90 | 3.49 | 79 | 4.44 | 3.47 | -0.66 | 0.38 | .086 | .19 | -0.48 | 0.42 | .249 | .14 |
| Self-managed intervention | 85 | 4.40 | 3.54 | 78 | 3.99 | 3.45 | 76 | 4.05 | 3.43 | -0.18 | 0.39 | .636 | .05 | -0.49 | 0.42 | .240 | .14 |
| Control ‡ | 84 | 4.50 | 3.54 | 80 | 4.27 | 3.49 | 79 | 4.64 | 3.48 | | | | | | | | |
| **Psychological distress** | | | | | | | | | | | | | | | | | |
| HADS total (p = .296#) | | | | | | | | | | | | | | | | | |
| Guided intervention | 85 | 11.85 | 6.85 | 81 | 9.66 | 6.74 | 79 | 10.97 | 6.69 | -1.35 | 0.70 | .055 | .20 | -0.70 | 0.74 | .345 | .10 |
| Self-managed intervention | 85 | 10.76 | 6.85 | 78 | 9.36 | 6.67 | 76 | 9.68 | 6.62 | -0.56 | 0.71 | .431 | .08 | -0.90 | 0.75 | .231 | .13 |
| Control ‡ | 84 | 11.35 | 6.85 | 80 | 10.51 | 6.74 | 79 | 11.17 | 6.72 | | | | | | | | |
| **Physical functioning** | | | | | | | | | | | | | | | | | |
| SF-36 physical functioning (p = .811#) | | | | | | | | | | | | | | | | | |
| Guided intervention | 85 | 77.94 | 19.61 | 81 | 79.42 | 19.30 | 79 | 79.49 | 19.19 | 2.18 | 1.97 | .269 | .11 | 2.18 | 2.26 | .335 | .11 |
| Self-managed intervention | 85 | 80.94 | 19.61 | 79 | 81.08 | 19.15 | 76 | 81.91 | 18.98 | 0.84 | 1.98 | .672 | .04 | 1.60 | 2.28 | .482 | .08 |
| Control ‡ | 84 | 78.27 | 19.61 | 80 | 77.58 | 19.31 | 79 | 77.64 | 19.27 | | | | | | | | |

(continued on following page)

**Table 3.** Between group difference in mean change from baseline to follow-up (continued)

| | T0 | | | T1 | | | T2 | | | Between group difference T0-T1 | | | | Between group difference T0-T2 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD | N | Mean | SD | Mean change | SE | p | ES † | Mean change | SE | p | ES † |
| **Role limitations due to physical problems** | | | | | | | | | | | | | | | | | |
| SF-36 role physical (p = . 841#) | | | | | | | | | | | | | | | | | |
| Guided intervention | 85 | 60.00 | 38.68 | 81 | 69.41 | 38.36 | 79 | 61.97 | 38.20 | 1.44 | 5.60 | .797 | .04 | -2.13 | 5.80 | .714 | .06 |
| Self-managed intervention | 85 | 65.00 | 38.68 | 78 | 68.91 | 38.11 | 76 | 66.68 | 37.96 | -4.05 | 5.64 | .473 | .10 | -2.41 | 5.84 | .680 | .06 |
| Control ‡ | 84 | 61.61 | 38.68 | 80 | 69.57 | 38.14 | 79 | 65.70 | 38.31 | | | | | | | | |
| **Bodily pain** | | | | | | | | | | | | | | | | | |
| SF-36 bodily pain (p = .854#) | | | | | | | | | | | | | | | | | |
| Guided intervention | 85 | 65.12 | 22.76 | 81 | 65.92 | 22.53 | 79 | 66.86 | 22.40 | 1.65 | 3.01 | 0.58 | .07 | 2.24 | 3.06 | .466 | .10 |
| Self-managed intervention | 85 | 66.51 | 22.76 | 79 | 68.72 | 22.41 | 76 | 68.73 | 22.21 | 3.06 | 3.02 | 0.31 | .13 | 2.72 | 3.09 | .379 | .12 |
| Control ‡ | 84 | 67.56 | 22.76 | 80 | 66.72 | 22.54 | 79 | 67.07 | 22.47 | | | | | | | | |
| **General health perceptions** | | | | | | | | | | | | | | | | | |
| SF-36 general health (p = .716#) | | | | | | | | | | | | | | | | | |
| Guided intervention | 85 | 62.75 | 21.54 | 81 | 63.76 | 21.23 | 79 | 62.79 | 21.13 | 1.78 | 2.32 | .444 | .08 | 2.43 | 2.73 | .375 | .11 |
| Self-managed intervention | 85 | 61.77 | 21.54 | 79 | 62.19 | 21.08 | 76 | 62.94 | 20.93 | 1.20 | 2.34 | .609 | .06 | 3.57 | 2.75 | .196 | .17 |
| Control ‡ | 84 | 64.40 | 21.54 | 80 | 63.63 | 21.24 | 79 | 62.01 | 21.22 | | | | | | | | |
| **Vitality** | | | | | | | | | | | | | | | | | |
| SF-36 vitality (p = .148#) | | | | | | | | | | | | | | | | | |
| Guided intervention | 85 | 53.90 | 18.16 | 81 | 60.82 | 17.94 | 79 | 58.94 | 17.82 | 5.22 | 2.20 | .018 | .29 | 4.53 | 2.28 | .048 | .25 |
| Self-managed intervention | 85 | 56.55 | 18.16 | 79 | 60.69 | 17.83 | 76 | 60.30 | 17.66 | 2.45 | 2.21 | .270 | .13 | 3.24 | 2.30 | .160 | .18 |
| Control ‡ | 84 | 55.54 | 18.16 | 80 | 57.23 | 17.94 | 79 | 56.05 | 17.89 | | | | | | | | |

(continued on following page)

**Table 3.** Between group difference in mean change from baseline to follow-up (continued)

| | T0 | | | T1 | | | T2 | | | Between group difference T0-T1 | | | | Between group difference T0-T2 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD | N | Mean | SD | Mean change | SE | p | ES † | Mean change | SE | p | ES † |
| **Social functioning II** | | | | | | | | | | | | | | | | | |
| SF-36 social functioning (p = .224#) | | | | | | | | | | | | | | | | | |
| Guided intervention | 85 | 74.30 | 21.75 | 81 | 81.96 | 21.52 | 79 | 78.68 | 21.40 | 5.40 | 2.97 | .070 | .26 | 1.89 | 2.89 | .515 | .09 |
| Self-managed intervention | 85 | 80.25 | 20.59 | 79 | 81.63 | 20.36 | 76 | 83.39 | 20.16 | -0.88 | 2.95 | .765 | .04 | 0.64 | 2.88 | .824 | .03 |
| Control ‡ | 84 | 77.61 | 20.51 | 80 | 79.88 | 20.35 | 79 | 80.11 | 20.27 | | | | | | | | |
| **Role limitations due to emotional problems** | | | | | | | | | | | | | | | | | |
| SF-36 role emotional (p = .937#) | | | | | | | | | | | | | | | | | |
| Guided intervention | 85 | 75.29 | 34.36 | 81 | 79.36 | 34.23 | 79 | 75.38 | 34.16 | -0.70 | 5.97 | .906 | .02 | 2.40 | 6.09 | .694 | .07 |
| Self-managed intervention | 85 | 77.26 | 34.36 | 79 | 80.49 | 34.17 | 76 | 78.74 | 34.06 | -1.53 | 6.00 | .799 | .04 | 3.80 | 6.13 | .536 | .11 |
| Control ‡ | 84 | 77.78 | 34.36 | 80 | 82.55 | 34.24 | 79 | 75.46 | 34.21 | | | | | | | | |
| **Mental health** | | | | | | | | | | | | | | | | | |
| SF-36 mental health (p = .223#) | | | | | | | | | | | | | | | | | |
| Guided intervention | 85 | 72.82 | 16.46 | 81 | 77.77 | 16.26 | 79 | 75.29 | 16.16 | 3.42 | 1.99 | .087 | .21 | 3.28 | 2.12 | .124 | .20 |
| Self-managed intervention | 85 | 75.82 | 16.46 | 79 | 76.98 | 16.16 | 76 | 76.88 | 16.02 | -0.38 | 2.00 | .850 | .02 | 1.86 | 2.14 | .384 | .11 |
| Control ‡ | 84 | 73.82 | 16.46 | 80 | 75.35 | 16.26 | 79 | 73.01 | 16.23 | | | | | | | | |

**Table 3.** Between group difference in mean change from baseline to follow-up (continued)

Note: Reported means, standard deviations and effect sizes are model-based. Bold font indicates significant overall group by time interaction (p<.05) and significant contrasts (p<.01). When a significant overall interaction effect was observed, specific contrasts were evaluated. In the analysis, contrasts were based on the between group differences in mean change from baseline to follow-up (i.e. differences between the control group and the two intervention groups in mean change from T0 to T1 and from T0 to T2). The statistical model did not compare mean change between T1 and T2.

Abbreviations: FACT-ES, Functional Assessment of Cancer Therapy - Endocrine Symptoms (ranging from 0 - 72, higher scores indicate fewer menopausal symptoms); GSQS, Groningen Sleep Quality Scale (ranging from 0 - 14, higher scores indicate lower sleep quality); HADS, Hospital Anxiety and Depression Scale (anxiety and depression subscales range from 0 - 21, higher scores indicate more anxiety and depression; psychological distress ranging from 0 - 42, higher scores indicate more psychological distress); HF/NS, hot flushes/night sweats; HFRS, Hot Flush Rating Scale (problem rating subscale ranging from 0 - 10, higher scores indicate higher perceived impact of HF/NS; frequency subscales, weekly frequency of HF/NS); SAQ, Sexual Activity Questionnaire (sexual pleasure subscale ranging from 0 - 18, higher scores indicate higher levels of sexual pleasure; discomfort subscale ranging from 0 - 6, lower scores indicate lower levels of discomfort; habit subscale, ranging from 0 - 3, higher scores indicate more sexual activity); SD, standard deviation; SE, standard error; SF-36, Short Form Health Survey (all subscales range from 0 - 100, higher scores indicate higher levels of functioning/well-being); T0, baseline assessment; T1, short-term follow-up assessment at 10 weeks post-randomization; T2, longer-term follow-up assessment at 24 weeks post-randomization.

# p value of the overall time by group interaction.

† Effect size, based on the between group-difference in mean change and pooled SD of the intervention and control groups (.20 is considered small, .50 moderate/clinically significant and .80 large).

‡ Control group is reference category.

§Scale was completed by fewer than total No. of participants because it was relevant only for women who had had vaginal penetration.

II Model adjusted for surgery type.

We also calculated patient-level clinically significant improvement as determined by a 2-point (1 SD) difference on the HFRS problem rating scale because this had been used in previous trials by the authors of the HFRS [27, 28]. However, this is a stringent criterion for clinical significance compared with the criterion typically used in patient-reported outcome assessments (0.5 SD) [59] and may have resulted in an underestimation of the percentages of women with clinically significant improvement.

Our trial had several limitations. First, it would have been desirable to make a direct comparison between the efficacy of our iCBT with group-based, face-to-face CBT. Funding and resulting sample size limitations prohibited us from doing so. Second, although our results tend to support the literature regarding incrementally better compliance rates and stronger effects for guided versus self-managed iCBT programs, our sample size per group did not allow us to compare these program variants directly [32, 40, 41]. To do so would have required a much larger sample size (175 patients per study arm) to have sufficient power (80%) to detect (realistically) smaller between-group differences in key outcomes (ES, .30) [57]. Finally, although the ability to compare the results of our trial with those of other types of interventions for menopausal symptoms (e.g., medications or acupuncture) would be desirable, such a comparison is hampered by the fact that CBT is intended primarily to help women cope with their symptoms and, thus, lessen the impact of their symptoms (perceived burden) and is evaluated in those terms, whereas other treatments are intended primarily to reduce the frequency of symptoms. Our study also had a number of important strengths, including the RCT design, the multicenter participation, use of standardized outcome measures, and the high follow-up rates.

In conclusion, our findings indicate that iCBT, with or without therapist support, has a positive effect on the perceived impact of HF/NS, overall levels of menopausal symptoms, sleep quality and frequency of HF/NS. Although results favored the guided over the self-managed group, this advantage should be weighed against the additional costs of the guided version of the program. Future analyses are planned to evaluate the cost effectiveness of the interventions and to identify patient-related moderating factors that enhance or detract from their efficacy.

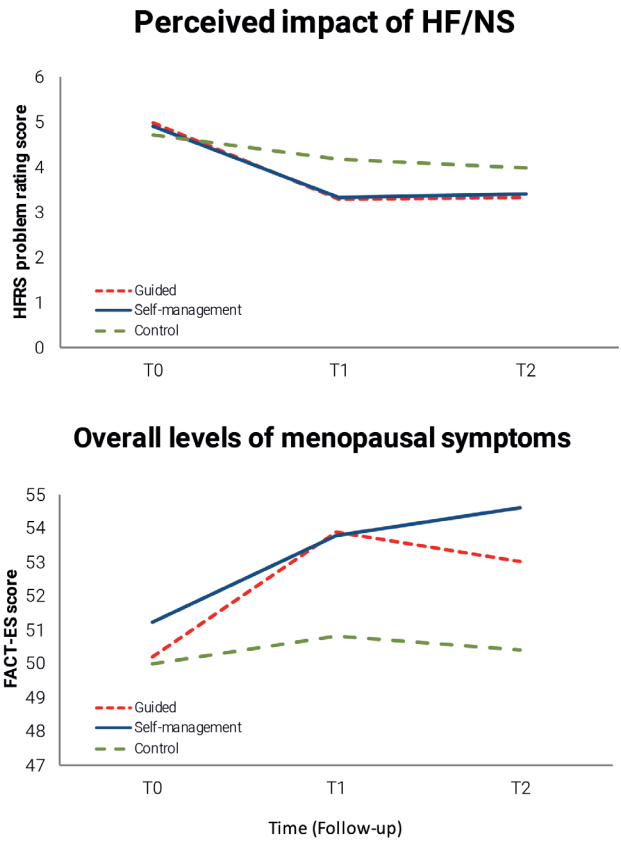



**Figure 2.** Mean values of hot flushes and night sweats (HF/NS) problem rating and overall levels of menopausal symptoms. Higher scores on the problem rating subscale of the Hot Flush Rating Scale (HFRS) indicate a higher perceived impact of HF/NS. Higher scores on the Functional Assessment of Cancer Treatment-Endocrine Symptoms (FACT-ES) indicate lower overall levels of menopausal symptoms.
Abbreviations: HF/NS, hot flushes / night sweats; T0, baseline; T1, follow-up assessment at 10 weeks; T2, follow-up assessment at 24 weeks.

## REFERENCES


[1] J. Bines, D.M. Oleske, M.A. Cobleigh, Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer, J Clin Oncol 14(5) (1996) 1718-1729.

[2] C.L. Shapiro, A. Recht, Side effects of adjuvant treatment of breast cancer., N Engl J Med 344(26) (2001) 1997-2008.

[3] J.B. Madalinska, M. Van Beurden, E.M. Bleiker, H.B. Valdimarsdottir, J. Hollenstein, L.F. Massuger, K.N. Gaarenstroom, M.J. Mourits, R.H. Verheijen, E.B. Van Dorst, H. Van der Putten, K. Van der Velden, H. Boonstra, N.K. Aaronson, The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women after prophylactic salpingo-oophorectomy, J.Clin.Oncol. 24(22) (2006) 3576-3582.

[4] S.M. Rosenberg, A.H. Partridge, Premature menopause in young breast cancer: effects on quality of life and treatment interventions, J Thorac Dis 5(Suppl 1) (2013) S55-S61.

[5] P.J. Goodwin, M. Ennis, K.I. Pritchard, M. Trudeau, N. Hood, Risk of menopause during the first year after breast cancer diagnosis., J Clin Oncol 17(8) (1999) 2365-2370.

[6] C.H. Mom, C. Buijs, P.H. Willemse, M.J. Mourits, E.G. de Vries, Hot flushes in breast cancer patients, Critical reviews in oncology/hematology 57(1) (2006) 63-77.

[7] M.S. Hunter, E.A. Grunfeld, S. Mittal, P. Sikka, A.J. Ramirez, I. Fentiman, H. Hamed, Menopausal symptoms in women with breast cancer: prevalence and treatment preferences., Psychooncology 13(11) (2004) 769-778.

[8] J.S. Carpenter, M.A. Andrykowski, Menopausal symptoms in breast cancer survivors., Oncol Nurs Forum 26(8) (1999) 1311-1317.

[9] P. Gupta, D.W. Sturdee, S.L. Palin, K. Majumder, R. Fear, T. Marshall, I. Paterson, Menopausal symptoms in women treated for breast cancer: the prevalence and severity of symptoms and their perceived effects on quality of life, Climacteric 9(1) (2006) 49-58.

[10] J.R. Bloom, S.L. Stewart, S. Chang, P.J. Banks, Then and now: quality of life of young breast cancer survivors, Psychooncology 13(3) (2004) 147-160.

[11] R.J. Couzi, K.J. HelzIsouer, J.H. Fetting, Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes toward estrogen replacement therapy., J Clin Oncol 13(11) (1995) 2737-2744.

[12] J.S. Carpenter, M.A. Andrykowski, M. Cordova, L. Cunningham, J. Studts, P. McGrath, D. Kenady, D. Sloan, R. Munn, Hot flashes in postmenopausal women treated for breast carcinoma - Prevalence, severity, correlates, management, and relation to qualify of life, Cancer 82(9) (1998) 1682-1691.

[13] J.L. Marino, C.M. Saunders, L.I. Emery, H. Green, D.A. Doherty, M. Hickey, Nature and severity of menopausal symptoms and their impact on quality of life and sexual function in cancer survivors compared with women without a cancer history, Menopause 21(3) (2014) 267-74.

[14] N.E. Avis, S. Crawford, J. Manuel, Psychosocial problems among younger women with breast cancer, Psychooncology 13(5) (2004) 295-308.
[15] Z. Moon, M.S. Hunter, R. Moss-Morris, L.D. Hughes, Factors related to the experience of menopausal symptoms in women prescribed tamoxifen, J Psychosom Obstet Gynaecol (2016) 1-10.
[16] T.I. Barron, R. Connolly, K. Bennett, J. Feely, M.J. Kennedy, Early discontinuation of tamoxifen: a lesson for oncologists, Cancer 109(5) (2007) 832-839.
[17] C.C. Murphy, L.K. Bartholomew, M.Y. Carpentier, S.M. Bluethmann, S.W. Vernon, Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review, Breast Cancer Res Treat 134(2) (2012) 459-78.
[18] D. Stan, C.L. Loprinzi, K.J. Ruddy, Breast cancer survivorship issues, Hematology/oncology clinics of North America 27(4) (2013) 805-27, ix.
[19] H.D. Nelson, K.K. Vesco, E. Haney, R. Fu, A. Nedrow, J. Miller, C. Nicolaidis, M. Walker, L. Humphrey, Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis, Jama 295(17) (2006) 2057-71.
[20] K.J. Pandya, G.R. Morrow, J.A. Roscoe, H. Zhao, J.T. Hickok, E. Pajon, T.J. Sweeney, T.K. Banerjee, P.J. Flynn, Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial, Lancet 366(9488) (2005) 818-824.
[21] A.H. Boekhout, A.D. Vincent, O.B. Dalesio, J. van den Bosch, J.H. Foekema-Tons, S. Adriaansz, S. Sprangers, B. Nuijen, J.H. Beijnen, J.H. Schellens, Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: a randomized, double-blind, placebo-controlled trial, J Clin Oncol 29(29) (2011) 3862-3868.
[22] J.B. Hervik, T. Stub, Adverse effects of non-hormonal pharmacological interventions in breast cancer survivors, suffering from hot flashes: A systematic review and meta-analysis, Breast Cancer Res Treat 160(2) (2016) 223-236.
[23] M.S. Hunter, K.L.M. Liao, Evaluation of a four-session cognitive-behavioural intervention for menopausal hot flushes, Br. J. Health Psychol. 1 (1996) 113-125.
[24] M. Hunter, Cognitive behavioural interventions for premenstrual and menopausal symptoms, Journal of Reproductive and Infant Psychology 21(3) (2003) 183-193.
[25] M.S. Hunter, S. Coventry, H. Hamed, I. Fentiman, E.A. Grunfeld, Evaluation of a group cognitive behavioural intervention for women suffering from menopausal symptoms following breast cancer treatment, Psychooncology 18(5) (2009) 560-3.
[26] M.S. Hunter, E. Mann, A cognitive model of menopausal hot flushes and night sweats, J Psychosom Res 69(5) (2010) 491-501.
[27] B. Ayers, M. Smith, J. Hellier, E. Mann, M.S. Hunter, Effectiveness of group and self-help cognitive behavior therapy in reducing problematic menopausal hot flushes and night sweats (MENOS 2): a randomized controlled trial, Menopause 19(7) (2012) 749-759.

[28] E. Mann, M.J. Smith, J. Hellier, J.A. Balabanovic, H. Hamed, E.A. Grunfeld, M.S. Hunter, Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial, Lancet Oncol 13(3) (2012) 309-318.

[29] S.F.A. Duijts, M. Van Beurden, H.S.A. Oldenburg, M.S. Hunter, J.M. Kieffer, M.M. Stuiver, M.A. Gerritsma, M.B.E. Menke-Pluymers, P.W. Plaisir, H. Rijna, A.M.F. Lopes Cardozo, G.J. Timmers, S. Van der Meij, H. Van der Veen, N. Bijker, L.M. De Widt-Levert, M.M. Geenen, G. Heuff, E.J. Van Dulken, E. Boven, N.K. Aaronson, Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: Results of a randomized controlled multicenter trial., Journal of Clinical Oncology 30(33) (2012) 4124-4133.

[30] E. Stefanopoulou, M.S. Hunter, Telephone-guided Self-Help Cognitive Behavioural Therapy for menopausal symptoms, Maturitas 77(1) (2014) 73-7.

[31] A. Barak, L. Hen, M. Boniel-Nissim, N.a. Shapira, A Comprehensive Review and a Meta-Analysis of the Effectiveness of Internet-Based Psychotherapeutic Interventions, Journal of Technology in Human Services 26(2-4) (2008) 109-160.

[32] V. Spek, P. Cuijpers, I. Nyklicek, H. Riper, J. Keyzer, V. Pop, Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis, Psychol Med 37(3) (2007) 319-28.

[33] G. Andersson, Using the Internet to provide cognitive behaviour therapy, Behav. Res. Ther. 47(3) (2009) 175-180.

[34] P. Cuijpers, A. van Straten, G. Andersson, Internet-administered cognitive behavior therapy for health problems: A systematic review., J. Behav. Med. Vol.31(2) (2008) 169-177.

[35] Y. Leykin, S.M. Thekdi, D.M. Shumay, R.F. Munoz, M. Riba, L.B. Dunn, Internet interventions for improving psychological well-being in psycho-oncology: review and recommendations, Psychooncology 21(9) (2012) 1016-25.

[36] G. Bouma, J.M. Admiraal, E.G. de Vries, C.P. Schroder, A.M. Walenkamp, A.K. Reyners, Internet-based support programs to alleviate psychosocial and physical symptoms in cancer patients: a literature analysis, Critical reviews in oncology/hematology 95(1) (2015) 26-37.

[37] P. Carlbring, G. Andersson, P. Cuijpers, H. Riper, E. Hedman-Lagerlof, Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: an updated systematic review and meta-analysis, Cogn Behav Ther 47(1) (2018) 1-18.

[38] G. Andersson, P. Cuijpers, P. Carlbring, H. Riper, E. Hedman, Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis, World psychiatry : official journal of the World Psychiatric Association (WPA) 13(3) (2014) 288-95.

[39] G. Andrews, P. Cuijpers, M.G. Craske, P. McEvoy, N. Titov, Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: a meta-analysis, PLoS One 5(10) (2010) e13196.

[40] B. Palmqvist, P. Carlbring, G. Andersson, Internet-delivered treatments with or without therapist input: does the therapist factor have implications for efficacy and cost?, Expert review of pharmacoeconomics & outcomes research 7(3) (2007) 291-7.
[41] H. Baumeister, L. Reichler, M. Munzinger, J. Lin, The impact of guidance on Internet-based mental health interventions — A systematic review, Internet Interventions 1(4) (2014) 205-215.
[42] G. Alkhaldi, F.L. Hamilton, R. Lau, R. Webster, S. Michie, E. Murray, The Effectiveness of Prompts to Promote Engagement With Digital Interventions: A Systematic Review, Journal of medical Internet research 18(1) (2016) 14.
[43] N. Titov, B.F. Dear, L. Johnston, C. Lorian, J. Zou, B. Wootton, J. Spence, P.M. McEvoy, R.M. Rapee, Improving adherence and clinical outcomes in self-guided internet treatment for anxiety and depression: randomised controlled trial, PLoS One 8(7) (2013) e62873.
[44] G. Clarke, D. Eubanks, E. Reid, C. Kelleher, E. O'Connor, L.L. DeBar, F. Lynch, S. Nunley, C. Gullion, Overcoming depression on the Internet (ODIN) (2): A randomized trial of a self-help depression skills program with reminders, Journal of medical Internet research 7(2) (2005) 11.
[45] V. Atema, M. van Leeuwen, H.S.A. Oldenburg, M. van Beurden, M.S. Hunter, N.K. Aaronson, An Internet-based cognitive behavioral therapy for treatment-induced menopausal symptoms in breast cancer survivors: results of a pilot study, Menopause 24(7) (2017) 762-767.
[46] V. Atema, M. van Leeuwen, H.S. Oldenburg, V. Retel, M. van Beurden, M.S. Hunter, N.K. Aaronson, Design of a randomized controlled trial of Internet-based cognitive behavioral therapy for treatment-induced menopausal symptoms in breast cancer survivors, BMC Cancer 16(1) (2016) 920.
[47] M.S. Hunter, K.L.M. Liao, A psychological analysis of menopausal hot flushes, Br. J. Clin. Psychol. 34 (1995) 589-599.
[48] N.W. Scott, G.C. McPherson, C.R. Ramsay, M.K. Campbell, The method of minimization for allocation to clinical trials. a review., Control Clin Trials 23(6) (2002) 662-674.
[49] L.J. Fallowfield, S.K. Leaity, A. Howell, S. Benson, D. Cella, Assessment of quality of life in women undergoing hormonal therapy for breast cancer: validation of an endocrine symptom subscale for the FACT-B, Breast Cancer Res Treat 55(2) (1999) 189-199.
[50] S. Jafarian, F. Gorouhi, A. Taghva, J. Lotfi, High-altitude sleep disturbance: results of the Groningen Sleep Quality Questionnaire survey, Sleep medicine 9(4) (2008) 446-9.
[51] A. de Weerd, S. de Haas, A. Otte, D.K. Trenite, G. van Erp, A. Cohen, M. de Kam, J. van Gerven, Subjective sleep disturbance in patients with partial epilepsy: a questionnaire-based study on prevalence and impact on quality of life, Epilepsia 45(11) (2004) 1397-1404.
[52] K. Thirlaway, L. Fallowfield, J. Cuzick, The Sexual Activity Questionnaire: a measure of women's sexual functioning, Qual Life Res 5(1) (1996) 81-90.

[53] A.S. Zigmond, R.P. Snaith, The hospital anxiety and depression scale, Acta Psychiatr Scand 67(6) (1983) 361-370.
[54] I. Bjelland, A.A. Dahl, T.T. Haug, D. Neckelmann, The validity of the Hospital Anxiety and Depression Scale - An updated literature review, Journal of Psychosomatic Research 52(2) (2002) 69-77.
[55] J.E. Ware, Jr., C.D. Sherbourne, The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection, Med Care 30(6) (1992) 473-83.
[56] N.K. Aaronson, M. Muller, P.D.A. Cohen, M.L. Essink-Bot, M. Fekkes, R. Sanderman, M.A.G. Sprangers, A.T. Velde, E. Verrips, Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations, Journal of Clinical Epidemiology 51(11) (1998) 1055-1068.
[57] J. Cohen, Statistical power analysis for the behavioral sciences, Lawrence Earlbaum Associates, Hillsdale, New Jersey, 1988.
[58] R.C. Littell, J. Pendergast, R. Natarajan, Modelling covariance structure in the analysis of repeated measures data, Statistics in medicine 19(13) (2000) 1793-819.
[59] G.R. Norman, J.A. Sloan, K.W. Wyrwich, Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation, Med Care 41(5) (2003) 582-592.
[60] D.L. Streiner, G.R. Norman, J. Cairney, Health measurement scales: a practical guide to their development and use, 5th ed., Oxford University Press Oxford, UK, 2014.
[61] W. van Ballegooijen, P. Cuijpers, A. van Straten, E. Karyotaki, G. Andersson, J.H. Smit, H. Riper, Adherence to Internet-Based and Face-to-Face Cognitive Behavioural Therapy for Depression: A Meta-Analysis, PLoS One 9(7) (2014) e100674.
[62] J. Chilcot, S. Norton, M.S. Hunter, Cognitive behaviour therapy for menopausal symptoms following breast cancer treatment: Who benefits and how does it work?, Maturitas 78(1) (2014) 56-61.

**Appendix: Table A1.** Study outcome measures and corresponding questionnaires

| Variable | Questionnaire | Details | Assessment |
|---|---|---|---|
| **Primary outcomes** | | | |
| Hot flush/ Night sweats problem rating | HFRS | • 3 items (subscale), 10 point scale<br>• Score range: 0 -10 (mean scores are used), higher scores indicate higher perceived impact<br>• Time frame: past week<br>• Test-retest reliability 0.79 | Screening, T0, T1, T2 |
| Overall level of menopausal symptoms | FACT-ES | • 18 items, 4 point Likert scale<br>• Score range: 0 – 72; higher scores indicate fewer overall levels of menopausal symptoms<br>• Time frame: past week<br>• Cronbach's alpha: .79 | T0, T1, T2 |
| **Secondary outcomes** | | | |
| Sexual functioning | SAQ | • 10 items, 4 point Likert scale<br>• Subscales: pleasure; discomfort; habit<br>• Score range: pleasure 0 – 18 higher scores indicate higher levels of pleasure; discomfort 0 – 6 lower scores indicates lower levels of discomfort; habit 0 – 3; single item (0 'less sexual activity than usual' to 3 'much more sexual activity than usual'<br>• Time frame: past month<br>• Test-retest kappa: 0.50-0.76 | T0, T1, T2 |
| Sleep quality | GSQS | • 14 items, dichotomous (yes/no) scale<br>• Score range: 0 – 14; higher scores indicate more sleep problems<br>• Time frame: past month<br>• Chronbach's alpha: .90 | T0, T1, T2 |
| Hot flush and night sweats frequency | HFRS | • 2 items (one for hot flushes and one for night sweats)<br>• Score range: reported average of hot flushes and night sweats per week<br>• Time frame: past week<br>• Test-retest reliability 0.82 | T0, T1, T2 |

(continued on following page)

**Appendix: Table A1.** Study outcome measures and corresponding questionnaires (Continued)

| Variable | Questionnaire | Details | Assessment |
|---|---|---|---|
| Psychological distress | HADS | • 14 items, 4 point Likert scale<br>• Subscales: depression (HADS-D); anxiety (HADS-A)<br>• Score range: total score 0 – 42; subscale scores 0 – 21 higher score indicates more psychological distress<br>• Time frame: past week<br>• Cronbach's alpha: HADS-D 0.67-0.90; HADS-A 0.68-0.93 | T0, T1, T2 |
| Health-related quality of life | SF-36 | • 36 items, dichotomous and 3- to 6-point Likert scales<br>• Subscales: physical functioning, role limitations due to physical health problems, bodily pain, social functioning, general mental health, role limitations due to emotional problems, vitality, general health perceptions<br>• Score range: 0- 100; higher score indicates higher levels of functioning/ well-being<br>• Time frame: past week<br>• Cronbach's alpha: 0.66-0.93 (mean 0.84) | T0, T1, T2 |

Abbreviations: FACT-ES, Functional Assessment of Cancer Therapy - Endocrine Symptoms; GSQS, Groningen Sleep Quality Scale; HADS, Hospital Anxiety and Depression Scale; HF/NS, hot flushes/night sweats; HFRS, Hot Flush Rating Scale; SAQ, Sexual Activity Questionnaire; SF-36, Short Form Health Survey; T0, baseline; T1, follow-up 1; T2, follow-up 2.

CHAPTER 5

# COST-UTILITY, COST-EFFECTIVENESS, AND BUDGET IMPACT OF INTERNET-BASED COGNITIVE BEHAVIORAL THERAPY FOR BREAST CANCER SURVIVORS WITH TREATMENT-INDUCED MENOPAUSAL SYMPTOMS

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# ABSTRACT

## Purpose

Internet-based cognitive behavioral therapy (iCBT), with and without therapist support, is effective in reducing treatment-induced menopausal symptoms and perceived impact of hot flushes and night sweats (HF/NS) in breast cancer survivors. The aim of the current study was to evaluate the cost-utility, cost-effectiveness, and budget impact of both iCBT formats compared to a waiting list control group from the Dutch healthcare perspective.

## Methods

A Markov model was constructed with a 5-year time horizon. Costs and health outcomes were measured alongside a randomized controlled clinical trial and included quality-adjusted life years (QALYs), overall levels of menopausal symptoms, and perceived impact of HF/NS. Uncertainty was examined using probabilistic and deterministic sensitivity analyses, together with a scenario analysis incorporating a different perspective.

## Results

iCBT was slightly more expensive than the waiting list control, but also more effective, resulting in incremental cost-utility ratios of € 23,331 / QALY and € 11,277 / QALY for the guided and self-managed formats, respectively. A significant reduction in overall levels of menopausal symptoms or perceived impact of HF/NS resulted in incremental costs between € 1,460 - € 1,525 for the guided and € 500 - € 753 for the self-managed format. The estimated annual budget impact for the Netherlands was € 192,990 for the guided and € 74,592 for the self-managed format.

## Conclusion

Based on the current trial data, the results indicate that both guided and self-managed iCBT are cost-effective with a willingness-to-pay threshold of well below € 30,000 / QALY. Additionally, self-managed iCBT is the most cost-effective strategy and has a lower impact on healthcare budgets.

## INTRODUCTION

Adjuvant treatments for breast cancer (BC), including chemotherapy, endocrine therapy, and oophorectomy can lead to treatment-induced menopausal symptoms [1, 2]. These symptoms, and in particular hot flushes and night sweats (HF/NS), negatively affect health-related quality of life (HRQL) [3-5] and cause some women to discontinue their endocrine treatments [6, 7]. Although medications such as gabapentin, clonidine, and antidepressants are moderately effective in reducing HF/NS, they are accompanied by bothersome side effects [8-11]. In contrast, cognitive behavioral therapy (CBT) programs are without side effects, are effective, and are favored by BC survivors [12-16].

CBT programs have often been delivered in group format [14-16]. However, BC survivors have reported practical and scheduling barriers to attending such group sessions [16]. Therefore, these programs have been translated into an online format [17, 18]. Our recent randomized controlled trial (RCT) comparing Internet-based CBT (iCBT), with and without therapist support, with a waiting list control group demonstrated that women allocated to iCBT experienced a greater reduction in overall levels of menopausal symptoms and perceived impact of HF/NS. Significant reductions in the frequency of HF/NS and improvement in sleep quality were also observed [19]. When asked about preferences for a specific format, only a minority of women showed a strong preference for guided (16%) or self-managed (21%) iCBT. Although the magnitude of the effects favored the guided over the self-managed iCBT group, the former is associated with higher costs due to the added therapist support.

The observed differences in effectiveness and costs between the iCBT formats and the reality of budget restrictions underscore the need for an economic evaluation to assist policymakers in deciding whether to allocate healthcare resources to this program. Moreover, it may also guide practitioners in choosing which specific format to adopt [20]. Although a previous study by Mewes et al. [21] indicated that face-to-face group-based CBT was cost-effective, it is unknown whether online delivered CBT will lead to favorable cost-effectiveness ratios as well. Moreover, there are no studies reporting the budget impact of iCBT for treatment-induced menopausal symptoms, commonly used to estimate the impact on national, regional, or local health budget plans [22].

The objective of the current study was to evaluate the cost-utility and cost-effectiveness of guided and self-managed iCBT compared to a waiting list control group in terms of quality-adjusted life years (QALYs) and the primary clinical outcomes of the associated RCT (i.e. overall levels of menopausal symptoms and perceived impact of HF/NS), incorporating a healthcare perspective over a 5-year time period. An additional aim was to establish the estimated annual budget impact of implementing guided and/or self-managed iCBT in the Netherlands.

## METHODS

### Research design and study sample

A detailed description of the design, interventions, and outcomes of the RCT is provided elsewhere [18, 19]. Briefly, from 2015 to 2017, an RCT was conducted to evaluate the efficacy of iCBT, with and without therapist support, for treatment-induced menopausal symptoms in BC survivors. Patients were recruited from 12 hospitals in the Netherlands. Upon return of the informed consent and the baseline questionnaire (T0), 254 patients were randomized to a guided iCBT group, self-managed iCBT group, or a waiting list control group. Follow-up assessments were administered at 10 weeks (T1) and 24 weeks post-randomization (T2). All institutional review boards approved the study.

### Intervention and waiting list control group

All women randomized to the intervention groups had access to a 6-week iCBT program. A strong emphasis was placed on HF/NS, but other symptoms were also addressed. Women in the guided iCBT group received an additional telephone intake and weekly online feedback from a therapist. The average time-investment per therapist was 3 hours per patient. Participants allocated to the waiting list control group received usual care, which did not involve any form of care aimed at coping with menopausal symptoms.

### Measures

#### *Measurement and valuation of outcomes*

HRQOL was assessed using the 36-item Short Form Health Survey (SF-36 [23, 24]). To obtain utilities, scores on the eight scales were transformed

into a single EQ-5D utility score using the mapping algorithm of Ara and Brazier [25]. An additional algorithm was used to verify reliability of this conversion [26]. The EQ-5D utility scores can range between 0 and 1, with higher scores indicating better health. To calculate QALYs, we multiplied the derived utility scores with years of life (mortality rates) in the relevant health states.

The menopause-specific measures included overall levels of menopausal symptoms, as assessed by the Functional Assessment of Cancer Treatment-Endocrine Symptoms (FACT-ES [27]), and the perceived impact of HF/NS as assessed by the problem rating subscale of the Hot Flush Rating Scale (HFRS [28]). A clinically significant improvement was defined as a 0.5 standard deviation (SD) improvement for both measures [19, 27, 29, 30].

### *Measurement and valuation of costs*

Costs of the iCBT program were related to the online platform and therapist support. The online costs for the guided iCBT program were dependent on the number of therapists, irrespective of the number of patients, whereas the number of patients determined the online costs for the self-managed format. Valuations of the resources used were based on cost information provided by two potential providers of iCBT in the Netherlands, and invoices obtained during the RCT (e.g. hourly therapist rates).

Direct healthcare costs were measured during the RCT by the Dutch iMTA Medical Consumption Questionnaire (*i*MCQ [31]). Healthcare costs included the average number of visits to a range of healthcare providers (general practitioner, medical specialist, psychologist/psychiatrist, social worker, physiotherapist, lymphedema therapist, dietitian, and a practitioner of complementary alternative medicine). Valuation of visits to healthcare providers was based on the Dutch costing manual for economic evaluations [32, 33]. Mean per-patient resource use and valuation can be found in Table 1. Both types of costs (intervention and healthcare utilization) were applied in the healthcare perspective.

## Statistical analyses

### *Markov Model*

We adapted a previously developed and validated Markov model in Excel (Microsoft, Redmond, WA) in accordance with the Dutch guideline for health economic evaluations and international guidelines for modelling

(ISPOR-SMDM guidelines) [22, 33, 34]. A Markov model is a stochastic approach to modelling different states and the probabilities of transitions among them (Appendix A). The following four health states were defined in the current study: 1] experience of menopausal symptoms (based on inclusion criteria of the RCT); 2] reduction in menopausal symptoms; 3] cancer recurrence (local, regional or distant); and 4]death. Transition probabilities are displayed in Table 1. The transition probabilities between the first two health states were based on the percentage of women with a clinically significant improvement per trial arm on the FACT-ES as reported by Atema et al. [19]. Transition probabilities for local, regional, and distant metastases and corresponding increased mortality rate (MR), using age- and sex-specific mortality data, were based on data from Dutch registries [35, 36].

A hypothetical cohort of 1000 patients was used in the model with an average baseline age of 47, mirroring the mean age of participants at the start of the RCT. They were analysed over ten consecutive 6-month cycles in which the first cycle reflected the costs and effects of the iCBT as derived from the RCT [19]. The 5-year time horizon corresponds to the average duration of bothersome vasomotor symptoms of menopause [37]. The transition from health state 'menopausal symptoms' to 'reduction in menopausal symptoms' derived from the trial was only applied in the first cycle of the model. All other transitions remained applicable during consecutive cycles (Appendix A).

### *Cost-utility analysis*

Incremental cost-utility ratios (ICURs) of both formats of the iCBT were calculated as follows:

$$\text{ICUR} = \frac{\text{(Costs of the intervention group – costs of the waitlist control group)}}{\text{(QALYs of the intervention group – QALYs of the waitlist control group)}}$$

The diversity of willingness-to-pay (WTP) thresholds among countries shows that there is no uniformly accepted value. However, the World Health Organization has proposed a WTP threshold of one to three times the annual GDP per capita [38, 39]. Therefore, we estimated a WTP ceiling ratio of €30,000 per QALY for this study. Effects were discounted at 1.5% and costs at 4% annually as recommended by the Dutch costing manual [33].

### *Cost-effectiveness analysis*

We also performed a cost-effectiveness analysis using the principles of number needed to treat (NNT). NNT expresses how many patients, on average, need to be treated for one less adverse event or improvement of disease to be observed at a specific point in time [40, 41]. To calculate NNT and associated costs we used the following formulas:

The incremental costs to treat one patient reflects the costs per person of guided or self-managed iCBT over a 5-year period multiplied by the NNT to obtain one clinically significant reduction on the FACT-ES or HFRS problem rating scale.

### *Budget impact analysis*

We performed the budget impact analysis (BIA) in accordance with ISPOR principles of good practice [22, 42]. The incremental costs were calculated using the same assumptions and model that we developed for the cost-utility analysis. We then multiplied the incremental costs by the target population in the Netherlands, which we based on previous studies [35, 43-45]. We calculated that approximately 20% of the target population (3000 invasive BC cases in women aged ≤ 50 years) will start to use the iCBT program when offered in routine care, which corresponds to 600 patients per year in the Netherlands [35]. Therefore, the current BIA reflects the annual budget impact on the Dutch healthcare system.



### *Sensitivity analyses*

We used probabilistic sensitivity analysis (PSA) to estimate the uncertainty of the input parameters of the model using 5000 Monte Carlo simulations. We used Dirichlet, gamma, and beta distributions to estimate the uncertainty around transition probabilities, costs, and utilities, respectively. Uncertainty surrounding the ICURs was explored by plotting bootstrapped incremental cost-utility pairs on cost-effectiveness planes (CE-planes). A summary measure of the joint uncertainty of costs and effects for different thresholds was presented using cost-effectiveness acceptability curves (CEACs). CEACs indicate the intervention's probability of being cost-effective compared with the waiting list control group at different values of WTP. Additionally, we examined deterministic one-way sensitivity and structural uncertainty by addressing various assumptions regarding the model such as the duration of the treatment effects (from 5 to 3 years), different healthcare costs, QALYs, and intervention costs. Corresponding

parameters were based on the trial data (e.g. standard errors), ranging between two extreme yet plausible values. These analyses are displayed in tornado diagrams for both guided and self-managed iCBT separately.

We also conducted a scenario analysis in which we calculated cost-utility, cost-effectiveness, and budget impact from an intervention perspective by using only the intervention costs, meaning that we did not take into account healthcare utilization (e.g. general practitioner visits).

## RESULTS

### Costs and quality adjusted life years

Total intervention costs for guided and self-managed iCBT were € 226 and € 48 per patient, respectively (Table 1). At longer-term follow-up of the RCT, healthcare costs were higher in the 'Reduction in Menopausal' state as compared to the state 'Menopausal Symptoms' (Table 1). For a 5-year time horizon, total healthcare costs were € 5,315.55, € 5,118.22 and € 4,993.90 for guided iCBT, self-managed iCBT and the waiting list control group, respectively (Table 3).

The average 5-year QALY score was 4.119, 4.117 and 4.106 for guided iCBT, self-managed iCBT, and the waiting list control group, respectively (Table 3).

### Cost-utility analyses

The results indicated ICURs of € 23,331 / QALY and € 11,277 / QALY for guided and self-managed iCBT, respectively (Table 2). Descriptive CEACs and iCE planes are displayed in Figure 1 and 2, and described in the 'sensitivity analyses' section. For the intervention scenario, the ICURs were € 16,399 / QALY and € 4,346 / QALY for guided and self-managed iCBT, respectively.

**Table 1.** Input cost parameters in the MARKOV model

| Parameters | Mean | Standard error | Distribution | Source |
|---|---|---|---|---|
| **Utilities** | | | | |
| Menopausal symptoms | 0.83 | 0,013 | Beta | [19] |
| Reduction in menopausal symptoms | 0.85 | 0,017 | Beta | [19] |
| Recurrence | 0.73 | 0,020 | Beta | [54] |
| **Transition probabilities** | | | | |
| Menopausal symptoms to reduction in menopausal symptoms (guided iCBT) | 0.44 | - | Dirichlet | [19] |
| Menopausal symptoms to reduction in menopausal symptoms (self-managed iCBT) | 0.39 | - | Dirichlet | [19] |
| Menopausal symptoms to reduction in menopausal symptoms (waitlist control group iCBT) | 0.23 | - | Dirichlet | [19] |
| To recurrence from either state of menopausal symptoms or reduction in menopausal symptoms | 0.01 | - | Beta | [35] |
| Recurrence to death | 0.04 | - | Beta | [36] |
| Background mortality (age 47 to 51) | 0.0007-0.0012 | - | Fixed | |
| **Intervention costs^*** | | - | | |
| Online platform costs (guided iCBT) | € 12.59 | - | - | Practice |
| Online platform costs (self-managed iCBT) | € 33.28 | - | - | Practice |
| Training costs therapists | € 9.42 | - | - | Practice |
| Hourly rate therapist support (in total 3 hours needed to support patient) | € 135.00 | - | - | Practice |
| Total costs guided iCBT per patient without overhead costs | € 157.01 | - | - | Practice |
| Total costs self-managed iCBT per patient without overhead costs | € 33.28 | - | - | Practice |
| Total costs guided iCBT per patient with 44% overhead costs | € 226.09 | +/- 20% | Gamma | Practice |
| Total costs self-managed iCBT per patient with 44% overhead costs | € 47.92 | +/- 20% | Gamma | Practice |

(continued on following page)

**Table 1.** Input cost parameters in the MARKOV model (continued)

| | | | | |
|---|---|---|---|---|
| **Health care costs** | | | | |
| *Health state: menopausal symptoms* | | | | |
| General practitioner | € 48.70 | +/- 20% | Gamma | [19, 33] |
| Medical specialist | € 152.00 | +/- 20% | Gamma | [19, 33] |
| Psychologist or psychiatrist | € 35.20 | +/- 20% | Gamma | [19, 33] |
| Social worker | € 3.25 | +/- 20% | Gamma | [19, 33] |
| Physiotherapist | € 207.78 | +/- 20% | Gamma | [19, 33] |
| Lymphedema therapist | € 106.01 | +/- 20% | Gamma | [19, 33] |
| Dietitian | € 18.74 | +/- 20% | Gamma | [19, 33] |
| Alternative medicine | € 8.96 | +/- 20% | Gamma | [19, 33] |
| *Health state: Reduction in menopausal symptoms* | | | | |
| General practitioner | € 45.38 | +/- 20% | Gamma | [19, 33] |
| Medical specialist | € 129.28 | +/- 20% | Gamma | [19, 33] |
| Psychologist or psychiatrist | € 43.37 | +/- 20% | Gamma | [19, 33] |
| Social worker | € 9.47 | +/- 20% | Gamma | [19, 33] |
| Physiotherapist | € 158.05 | +/- 20% | Gamma | [19, 33] |
| Lymphedema therapist | € 93.75 | +/- 20% | Gamma | [19, 33] |
| Dietitian | € 4.99 | +/- 20% | Gamma | [19, 33] |
| Alternative medicine | € 19.11 | +/- 20% | Gamma | [19, 33] |
| *Health state: Recurrence‡* | | | | |
| Frist year: in- and outpatient costs | € 10,263.00 | +/- 20% | Gamma | [55] |
| First year: drug costs | € 1,918.00 | +/- 20% | Gamma | [55] |
| Second year: in- and outpatient costs | € 2,294.00 | +/- 20% | Gamma | [55] |
| Second year: drug costs | € 65.00 | +/- 20% | Gamma | [55] |

Abbreviations: iCBT, Internet-based cognitive behaviour therapy.
^Assumption that 600 patients enrol in iCBT.
*Online platform costs are dependent on the therapists in the guided format, whereas these costs are dependent on the number of patients in the self-managed format.

**Table 2.** Deterministic incremental cost-utility results and budget impact analyses for the base-case (FACT-ES)

| | Costs | QALY | Incremental Costs | Incremental QALYs | ICER | BIA** |
|---|---|---|---|---|---|---|
| **Healthcare perspective** | | | | | | |
| Guided iCBT | € 5,315.55 | 4.119 | € 321.65 | 0.0138 | € 23,330.50 | € 192,990 |
| Self-managed iCBT | € 5,118.22 | 4.117 | € 124.32 | 0.01102 | € 11,277.63 | € 74,592 |
| Waiting list control * | € 4,993.90 | 4.106 | n/a | n/a | n/a | n/a |
| **Intervention perspective** | | | | | | |
| Guided iCBT | € 226.09 | 4.119 | € 226.09 | 0.0138 | € 16,399.45 | € 135,654 |
| Self-managed iCBT | € 47.92 | 4.117 | € 47.92 | 0.01102 | € 4,346.58 | € 28,752 |
| Waiting list control* | € 0.00 | 4.106 | n/a | n/a | n/a | n/a |

Abbreviations: BIA, budget impact analysis;FACT-ES, Functional Assessment of Cancer Therapy - Endocrine Symptoms; iCBT, Internet-based cognitive behavioural therapy; ICER, incremental cost-utility ratio; QALY, Quality Adjusted Life Year; n/a, not applicable.
*Guided and self-managed interventions are compared with waiting list control group.
**Estimated that 600 patients per year will use the intervention in the Netherlands.



## Cost-effectiveness analyses

NNT calculations indicated that relatively fewer patients needed to be treated to obtain a significant reduction in menopausal symptoms (FACT-ES) in the guided iCBT format compared to the self-managed format (4.74 vs 6.06) (Table 3). The associated costs were higher for the guided iCBT than for the self-managed iCBT (€ 322 vs € 124). Therefore, total incremental treatment costs to obtain a significant decrease in menopausal symptoms were smaller for the self-managed format than for the guided (€ 753 vs € 1,525). The same trend was observed for the intervention scenario in which incremental costs were lower for the self-managed than the guided iCBT (€ 290 vs € 1,072).

The NNT to accomplish a significant reduction in the perceived impact of HF/NS (HFRS problem rating scale) favoured the self-managed iCBT over the guided iCBT (4.54 vs 4.02) (Table 3). Again, total incremental costs to obtain a significant decrease in the perceived impact of HF/NS were smaller for the self-managed iCBT than for the guided iCBT (€ 500 vs € 1460). Results for the intervention scenario indicated a similar pattern in which the incremental costs for the self-managed iCBT were lower than for the guided format (€ 193 vs € 1,026).

**Table 3.** Incremental cost-effectiveness results using NNT

| | Guided iCBT | Self-managed iCBT |
|---|---|---|
| **Significant reduction on the FACT-ES*** | | |
| Number needed to treat (NNT) | 4.74 | 6.06 |
| Incremental intervention costs | € 226.09 | € 47.92 |
| Incremental total costs (total healthcare) | € 321.65 | € 124.32 |
| Total incremental costs to treat one patient (intervention perspective) | € 1,071.51 | € 290.39 |
| Total incremental costs to treat one patient (healthcare perspective) | € 1,524.62 | € 753.38 |
| **Significant reduction on the HFRS problem rating scale*** | | |
| Number needed to treat (NNT) | 4.54 | 4.02 |
| Incremental intervention costs | € 226.09 | € 47.92 |
| Incremental total costs (total healthcare) | € 321.65 | €124.32 |
| Total incremental costs to treat one patient (intervention perspective) | € 1,026.45 | € 192.64 |
| Total incremental costs to treat one patient (healthcare perspective) | € 1,460.29 | € 499.77 |

Abbreviations: NNT, number needed to treat; FACT-ES, Functional Assessment of Cancer Treatment- Endocrine symptoms; HFRS, Hot Flush Rating Scale.
*Waiting list control group is reference category.

## Budget impact analyses

The budget impact of treating the Dutch target population (assuming 600 patients) with guided iCBT would result in an annual net increase of € 192,990 of additional expenditure from the Dutch healthcare budget to the target population. The budget impact of self-managed iCBT would result in a net increase of € 74,592 (Table 2). Additionally, total health expenditure of implementing a 50/50 combination of the guided and self-managed iCBT in the Dutch setting would entail an additional cost of € 133,785. Results for the intervention scenario indicated a higher 1-year net increase for the guided and the self-managed iCBT € 135,654 and €28,752 respectively, and a net increase of €49,322 when implementing a combination of the guided and self-managed iCBT formats.

### Sensitivity analyses

The CEACs indicate that guided iCBT has a 60.5% probability of being cost-effective for a WTP of € 30,000 (Figure 1A). For self-managed iCBT this probability is 79.5% (Figure 1B). Moreover, the combined CEAC indicates that self-managed iCBT has a 68.9% of being superior over guided iCBT and waiting list control with a WTP of € 30,000 (Figure 1C). For the scenario analyses (intervention perspective) the probability of cost-effectiveness for self-managed and guided iCBT is 88.8% and 72.9%, respectively, when using a WTP of € 30,000 (data not shown). The iCE planes resulted in most iterations being in the North-East quadrant (around 90%), indicating that both guided and self-managed iCBT resulted in higher costs and more QALYs (Figure 2). Moreover, the point estimates indicated that it is likely that both self-managed and guided iCBT will be below the €30,000/QALY threshold. Results from an intervention perspective indicated a similar pattern, with an average probability of 92% of being in the North-East quadrant (data not shown). In the sensitivity analysis, the parameters of the costs and utilities associated with the states 'Menopausal Symptoms' and 'Reduction in Menopausal Symptoms' alongside the duration of intervention effects and transition probabilities showed the greatest influence on the ICER. The tornado diagrams show the impact of the uncertainty per input parameter (Figure 3).



## DISCUSSION

This is the first study to investigate the cost-utility, cost-effectiveness, and budget impact of iCBT to alleviate treatment-induced menopausal symptoms in BC survivors. The results show that both the guided and self-managed formats of iCBT are associated with a small gain in QALYs over a 5-year time horizon, a decrease in menopausal symptoms, and a decrease in perceived impact of HF/NS. These improvements were accompanied with an increase in costs due to additional intervention and healthcare costs. However, analyses showed that ICURs are well below the proposed international WTP threshold of € 30,000 / QALY for both formats [39]. The probability that the ICERs are considered acceptable ultimately depends on the willingness to pay for a clinically significant decrease in menopausal symptoms and/or perceived HF/NS.

Our results indicate that, to accomplish a significant reduction in overall levels of menopausal symptoms or perceived impact of HF/NS, an

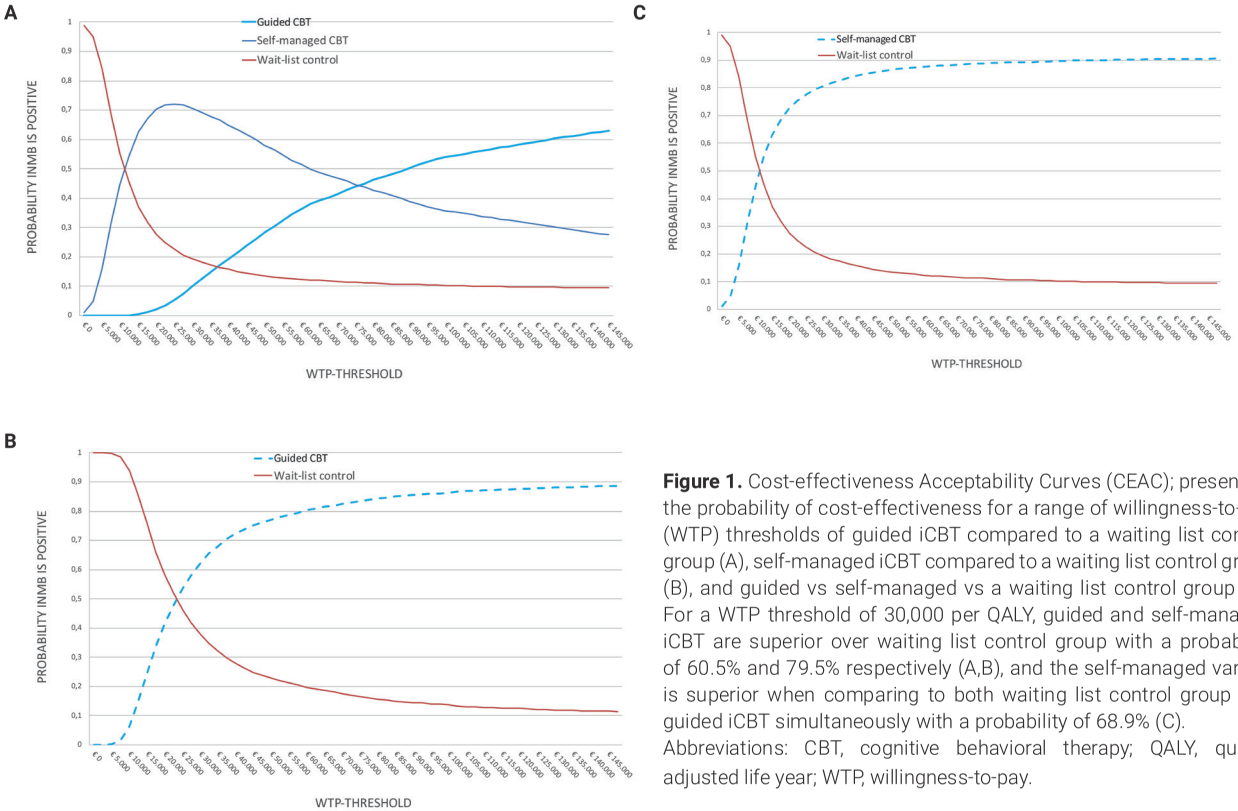



**Figure 1.** Cost-effectiveness Acceptability Curves (CEAC); presenting the probability of cost-effectiveness for a range of willingness-to-pay (WTP) thresholds of guided iCBT compared to a waiting list control group (A), self-managed iCBT compared to a waiting list control group (B), and guided vs self-managed vs a waiting list control group (C). For a WTP threshold of 30,000 per QALY, guided and self-managed iCBT are superior over waiting list control group with a probability of 60.5% and 79.5% respectively (A,B), and the self-managed variant is superior when comparing to both waiting list control group and guided iCBT simultaneously with a probability of 68.9% (C).
Abbreviations: CBT, cognitive behavioral therapy; QALY, quality adjusted life year; WTP, willingness-to-pay.

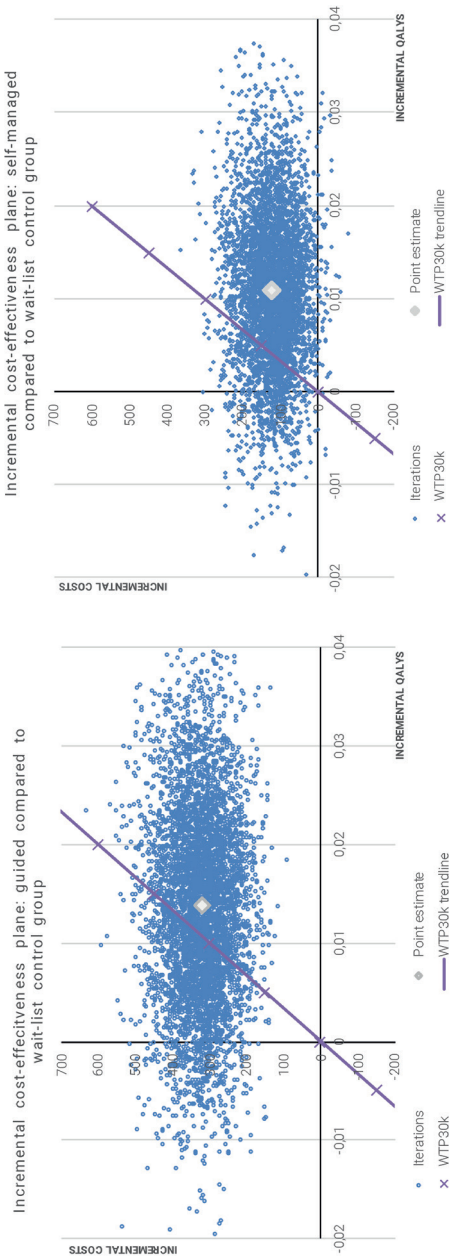
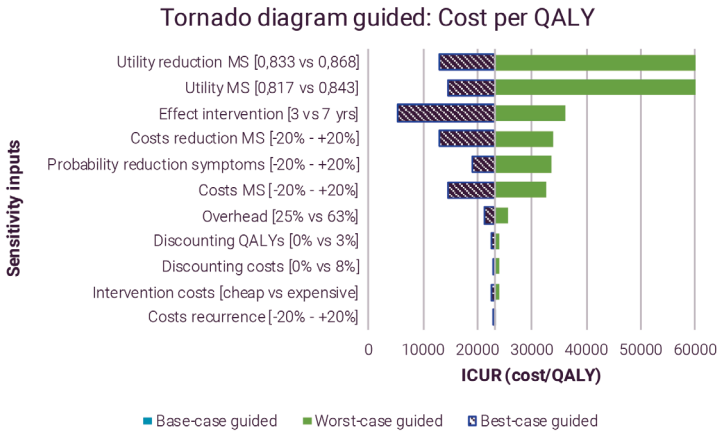



**Figure 2.** Incremental cost-effectiveness planes of the quality adjusted life years (QALYs) per costs of the guided and self-managed iCBT intervention groups compared to a waiting list control group. The scatter plots are showing the mean differences in costs and outcomes from the data using 5000 bootstrap replicates. Ninety-two and eighty-nine percent of the dots are in the North-East quadrant of the plane for the guided and self-managed interventions respectively. This indicates that there is a high probability that both treatments are more effective and more expensive compared to a waiting list control group.
Abbreviations: QALYs, quality adjusted life years, WTP, willingness-to-pay.

investment between € 1,026 - € 1,525 for the guided and € 193 - € 753 for the self-managed iCBT format will be necessary (the range reflects the perspective, i.e. only intervention costs, or intervention and healthcare costs). The annual Dutch budget impact (i.e. treating 600 patients) of implementing this program is estimated to be between € 74,592 and € 192,990 for the guided and between € 28,752 and € 74.592 for the self-managed iCBT. Additionally, sensitivity analyses showed that self-managed iCBT remains cost-effective (below the threshold of € 30,000 / QALY) for all variations in input parameters and assumptions, except when utility in the state 'Reduction in Menopausal Symptoms' decreases to its lower extreme value. For guided iCBT, shorter duration of intervention effects, increase in costs, decrease in utilities, and decrease in probability of obtaining a reduction in menopausal symptoms may result in unacceptable cost-effectiveness ratios, i.e. around € 35,000 / QALY or even higher ratios when utilities decrease unfavorably.

Compared to the economic evaluation of the group-based CBT program for alleviating menopausal symptoms in BC survivors [21], we observed similar costs per QALY outcomes for the guided format, but a reduction of more than € 10,000 / QALY for self-managed iCBT. We also observed higher incremental costs per clinically significant reduction in overall levels of menopausal symptoms and perceived impact of HF/NS for the guided format (+/- € 500), and lower incremental costs per clinically significant reduction for the self-managed iCBT, when compared with the group-based CBT format [21]. This indicates that an internet-delivered CBT program, particularly when self-managed, would be a viable alternative to face-to-face group sessions, with the added advantage of decreasing practical barriers as previously reported that hamper attendance at group sessions [16, 21]. In addition, the estimated budget impact is low in comparison to the total healthcare costs associated with the treatment of cancer in the Netherlands [46].

The increase in QALYs observed in our study and that of Mewes et al. [21] are relatively small. We believe this to be inherent to the aim of the current program, which is not primarily focused on improving overall HRQL, but rather on reducing overall levels of menopausal symptoms and perceived impact of HF/NS. When using a generic indicator of HRQL such as the SF-36, important gains in more specific domains are often missed due to the lack of responsiveness of the instrument [47], hence explaining the results from the deterministic sensitivity analysis. Therefore, cost-utility analyses



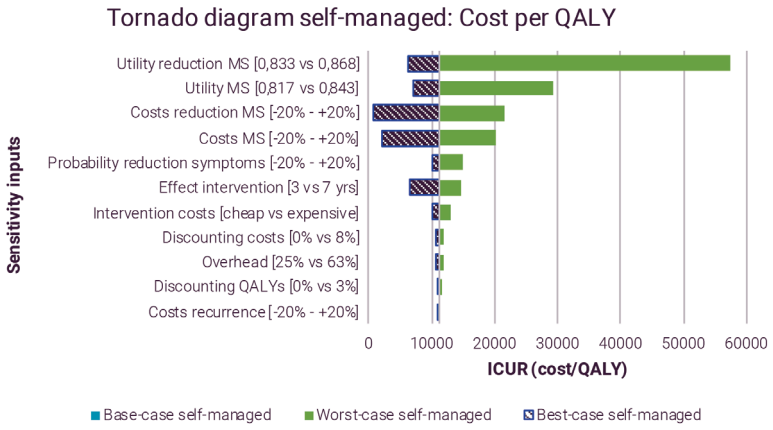




**Fig. 3** Tornado diagrams. This figure presents several univariate sensitivity analyses for both guided and self-managed iCBT. Parameters are ranked according to impact on incremental cost-utility ratio (ICUR). Results show that the utility attributed to the states 'Reduction in Menopausal Symptoms (MS)' and 'Menopausal Symptoms', the effect of the intervention lasting shorter/longer, transition probabilities, and the costs of states 'Reduction in Menopausal Symptoms' and 'Menopausal Symptoms' affect the ICUR the most. Moreover, self-managed iCBT seems to be more resistant to univariate differences in the model compared to guided iCBT.
Abbreviations: iCBT, Internet-based cognitive behavioral therapy; ICUR, incremental cost utility ratio; MS, menopausal symptoms; QALY(s), quality adjusted life year(s).

should be supplemented by cost-effectiveness analyses in which the cost per condition-specific outcome are measured and taken into account in reimbursement decisions. Moreover, we encourage the development and testing of condition-specific preference-based instruments which can be used within the QALY framework [47].

Based on our findings, we would recommend implementing the iCBT program according to a stepped care approach [48] in which the self-managed program serves as the primary treatment option. Dependent on available budgets, patient preferences and support needs, the iCBT program could be supplemented by therapist support. To keep the related costs of this guided format to a minimum, it is advisable to centralize the program within a limited number of treatment centers and have a relatively limited number of trained therapists. Future research is needed to be able to predict which women will benefit most from which format. Finally, as many BC survivors report a range of (interrelated) - psychosocial and physical problems [49-51], we would recommend efforts to combine and integrate various iCBT interventions (e.g., for cancer related fatigue, sleep problems, etc.) to better serve BC survivors and possibly reduce overall costs of psychosocial care in oncology settings.

This study has some limitations that should be noted. First, due to a lack of data, we did not include costs related to medication uptake. However, based on Mewes and colleagues [21], we expect these costs to be relatively low and similar across the intervention and control group. Second, we assessed healthcare consumption via generic questions that did not inquire specifically about the reason for utilization. It is likely that the differences in healthcare costs may not so much reflect the costs associated with the different formats of the iCBT program, but rather other factors. Third, there is increasing interest in conducting economic evaluations from a societal perspective, including costs associated with, among other things, productivity loss [52, 53]. While we had planned to include this perspective, it was evident to us that the productivity losses that were found during the trial could not be attributed to menopausal symptoms, but mainly to comorbid health conditions with which many BC survivors are faced. This study also had noteworthy strengths. These included the RCT design, multicenter participation, high response rates, including both a healthcare and intervention perspective, evaluating both cost-utility, cost-effectiveness and budget impact, and incorporating the intervention specific endpoints.

This economic evaluation of guided and self-managed iCBT supports its cost-effectiveness in three respects. First, the cost-utility analysis indicates a cost per QALY well below frequently used thresholds. Second, the cost to obtain a clinically relevant reduction of menopausal symptoms and/or perceived impact of HF/NS is modest for both formats. Third, the budget impact of both programs is negligible when compared to the total healthcare expenditure for treating cancer in the Netherlands. Additionally, while treatment effects were only slightly greater in the guided format, the self-managed format was associated with substantially lower costs and more stable results when testing various assumptions and/or parameters in sensitivity analyses. Taken together, our results tend to favor the self-managed version of the iCBT program over the guided format, and thus we would favor a stepped care approach in which the self-managed version of the program is the default option, with the guided version being reserved for those situations where women have a strong preference for such support and where sufficient funding is available for the additional costs involved.

## REFERENCES


[1] J. Bines, D.M. Oleske, M.A. Cobleigh, Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer, J Clin Oncol 14(5) (1996) 1718-1729.

[2] C.L. Shapiro, A. Recht, Side effects of adjuvant treatment of breast cancer., N Engl J Med 344(26) (2001) 1997-2008.

[3] J.S. Carpenter, M.A. Andrykowski, Menopausal symptoms in breast cancer survivors., Oncol Nurs Forum 26(8) (1999) 1311-1317.

[4] P. Gupta, D.W. Sturdee, S.L. Palin, K. Majumder, R. Fear, T. Marshall, I. Paterson, Menopausal symptoms in women treated for breast cancer: the prevalence and severity of symptoms and their perceived effects on quality of life, Climacteric 9(1) (2006) 49-58.

[5] Z. Moon, M.S. Hunter, R. Moss-Morris, L.D. Hughes, Factors related to the experience of menopausal symptoms in women prescribed tamoxifen, J Psychosom Obstet Gynaecol (2016) 1-10.

[6] C.C. Murphy, L.K. Bartholomew, M.Y. Carpentier, S.M. Bluethmann, S.W. Vernon, Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review, Breast Cancer Res Treat 134(2) (2012) 459-78.

[7] T.I. Barron, R. Connolly, K. Bennett, J. Feely, M.J. Kennedy, Early discontinuation of tamoxifen: a lesson for oncologists, Cancer 109(5) (2007) 832-839.

[8] D. Stan, C.L. Loprinzi, K.J. Ruddy, Breast cancer survivorship issues, Hematology/oncology clinics of North America 27(4) (2013) 805-27, ix.

[9] H.D. Nelson, K.K. Vesco, E. Haney, R. Fu, A. Nedrow, J. Miller, C. Nicolaidis, M. Walker, L. Humphrey, Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis, Jama 295(17) (2006) 2057-71.

[10] K.J. Pandya, G.R. Morrow, J.A. Roscoe, H. Zhao, J.T. Hickok, E. Pajon, T.J. Sweeney, T.K. Banerjee, P.J. Flynn, Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial, Lancet 366(9488) (2005) 818-824.

[11] A.H. Boekhout, A.D. Vincent, O.B. Dalesio, J. van den Bosch, J.H. Foekema-Tons, S. Adriaansz, S. Sprangers, B. Nuijen, J.H. Beijnen, J.H. Schellens, Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: a randomized, double-blind, placebo-controlled trial, J Clin Oncol 29(29) (2011) 3862-3868.

[12] M.S. Hunter, E.A. Grunfeld, S. Mittal, P. Sikka, A.J. Ramirez, I. Fentiman, H. Hamed, Menopausal symptoms in women with breast cancer: prevalence and treatment preferences., Psychooncology 13(11) (2004) 769-778.

[13] M.S. Hunter, K.L.M. Liao, Evaluation of a four-session cognitive-behavioural intervention for menopausal hot flushes, Br. J. Health Psychol. 1 (1996) 113-125.

[14] E. Mann, M.J. Smith, J. Hellier, J.A. Balabanovic, H. Hamed, E.A. Grunfeld, M.S. Hunter, Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial, Lancet Oncol 13(3) (2012) 309-318.
[15] B. Ayers, M. Smith, J. Hellier, E. Mann, M.S. Hunter, Effectiveness of group and self-help cognitive behavior therapy in reducing problematic menopausal hot flushes and night sweats (MENOS 2): a randomized controlled trial, Menopause 19(7) (2012) 749-759.
[16] S.F.A. Duijts, M. Van Beurden, H.S.A. Oldenburg, M.S. Hunter, J.M. Kieffer, M.M. Stuiver, M.A. Gerritsma, M.B.E. Menke-Pluymers, P.W. Plaisir, H. Rijna, A.M.F. Lopes Cardozo, G.J. Timmers, S. Van der Meij, H. Van der Veen, N. Bijker, L.M. De Widt-Levert, M.M. Geenen, G. Heuff, E.J. Van Dulken, E. Boven, N.K. Aaronson, Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: Results of a randomized controlled multicenter trial., Journal of Clinical Oncology 30(33) (2012) 4124-4133.
[17] V. Atema, M. van Leeuwen, H.S.A. Oldenburg, M. van Beurden, M.S. Hunter, N.K. Aaronson, An Internet-based cognitive behavioral therapy for treatment-induced menopausal symptoms in breast cancer survivors: results of a pilot study, Menopause 24(7) (2017) 762-767.
[18] V. Atema, M. van Leeuwen, H.S. Oldenburg, V. Retel, M. van Beurden, M.S. Hunter, N.K. Aaronson, Design of a randomized controlled trial of Internet-based cognitive behavioral therapy for treatment-induced menopausal symptoms in breast cancer survivors, BMC Cancer 16(1) (2016) 920.
[19] V. Atema, M. van Leeuwen, J.M. Kieffer, H.S.A. Oldenburg, M. van Beurden, M.A. Gerritsma, M.A. Kuenen, P.W. Plaisier, A.M.F. Lopes Cardozo, Y.E.A. van Riet, G. Heuff, H. Rijna, S. van der Meij, E.M. Noorda, G.J. Timmers, B.C. Vrouenraets, M. Bollen, H. van der Veen, N. Bijker, M.S. Hunter, N.K. Aaronson, Efficacy of Internet-Based Cognitive Behavioral Therapy for Treatment-Induced Menopausal Symptoms in Breast Cancer Survivors: Results of a Randomized Controlled Trial, J Clin Oncol 37(10) (2019) 809-22.
[20] A. Brennan, R. Akehurst, Modelling in health economic evaluation. What is its place? What is its value?, PharmacoEconomics 17(5) (2000) 445-59.
[21] J.C. Mewes, L.M. Steuten, S.F. Duijts, H.S. Oldenburg, M. van Beurden, M.M. Stuiver, M.S. Hunter, J.M. Kieffer, W.H. van Harten, N.K. Aaronson, Cost-effectiveness of cognitive behavioral therapy and physical exercise for alleviating treatment-induced menopausal symptoms in breast cancer patients, Journal of cancer survivorship : research and practice 9(1) (2015) 126-35.
[22] S.D. Sullivan, J.A. Mauskopf, F. Augustovski, J. Jaime Caro, K.M. Lee, M. Minchin, E. Orlewska, P. Penna, J.M. Rodriguez Barrios, W.Y. Shau, Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force, Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 17(1) (2014) 5-14.
[23] J.E. Ware, Jr., C.D. Sherbourne, The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection, Med Care 30(6) (1992) 473-83.

[24] N.K. Aaronson, M. Muller, P.D.A. Cohen, M.L. Essink-Bot, M. Fekkes, R. Sanderman, M.A.G. Sprangers, A.T. Velde, E. Verrips, Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations, Journal of Clinical Epidemiology 51(11) (1998) 1055-1068.

[25] R. Ara, J. Brazier, Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available), Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 11(7) (2008) 1131-43.

[26] D. Rowen, J. Brazier, J. Roberts, Mapping SF-36 onto the EQ-5D index: how reliable is the relationship?, Health and quality of life outcomes 7 (2009) 27.

[27] L.J. Fallowfield, S.K. Leaity, A. Howell, S. Benson, D. Cella, Assessment of quality of life in women undergoing hormonal therapy for breast cancer: validation of an endocrine symptom subscale for the FACT-B, Breast Cancer Res Treat 55(2) (1999) 189-199.

[28] M.S. Hunter, K.L.M. Liao, A psychological analysis of menopausal hot flushes, Br. J. Clin. Psychol. 34 (1995) 589-599.

[29] G.R. Norman, J.A. Sloan, K.W. Wyrwich, Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation, Med Care 41(5) (2003) 582-592.

[30] D.L. Streiner, G.R. Norman, J. Cairney, Health measurement scales: a practical guide to their development and use, 5th ed., Oxford University Press Oxford, UK, 2014.

[31] C. Bouwmans, K. De Jong, R. Timman, M. Zijlstra-Vlasveld, C. Van der Feltz-Cornelis, S. Tan Swan, L. Hakkaart-van Roijen, Feasibility, reliability and validity of a questionnaire on healthcare consumption and productivity loss in patients with a psychiatric disorder (TiC-P), BMC health services research 13 (2013) 217.

[32] J.B. Oostenbrink, M.A. Koopmanschap, F.F. Rutten, Standardisation of costs: the Dutch Manual for Costing in economic evaluations, PharmacoEconomics 20(7) (2002) 443-54.

[33] S.S. Tan, C.A. Bouwmans, F.F. Rutten, L. Hakkaart-van Roijen, Update of the Dutch Manual for Costing in Economic Evaluations, International journal of technology assessment in health care 28(2) (2012) 152-8.

[34] U. Siebert, O. Alagoz, A.M. Bayoumi, B. Jahn, D.K. Owens, D.J. Cohen, K.M. Kuntz, State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--3, Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 15(6) (2012) 812-20.

[35] Netherlands Comprehensive Cancer Organisation: Dutch Cancer Figures <https://www.cijfersoverkanker.nl/>, 2012 (accessed January 2019.).

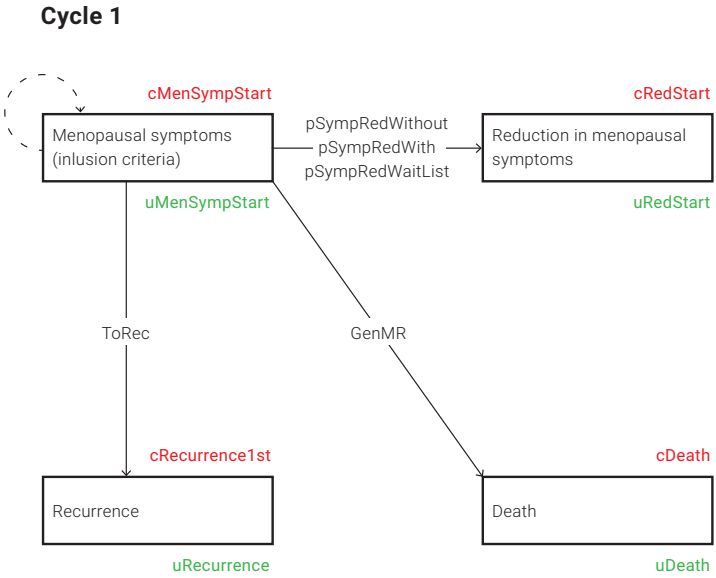
[36] Statistics Netherlands: Mortality statistics. <https://statline.cbs.nl/Statweb/>, 2014 (accessed January 2019.).

[37] S.R. Davis, M. Panjari, P.J. Robinson, P. Fradkin, R.J. Bell, Menopausal symptoms in breast cancer survivors nearly 6 years after diagnosis, Menopause 21(10) (2014) 1075-81.

[38] R. Schwarzer, U. Rochau, K. Saverno, B. Jahn, B. Bornschein, N. Muehlberger, M. Flatscher-Thoeni, P. Schnell-Inderst, G. Sroczynski, M. Lackner, I. Schall, A. Hebborn, K. Pugner, A. Fehervary, D. Brixner, U. Siebert, Systematic overview of cost-effectiveness thresholds in ten countries across four continents, Journal of comparative effectiveness research 4(5) (2015) 485-504.
[39] E. Marseille, B. Larson, D.S. Kazi, J.G. Kahn, S. Rosen, Thresholds for the cost-effectiveness of interventions: alternative approaches, Bulletin of the World Health Organization 93(2) (2015) 118-24.
[40] V. Garg, X. Shen, Y. Cheng, J.J. Nawarskas, D.W. Raisch, Use of number needed to treat in cost-effectiveness analyses, Ann Pharmacother 47(3) (2013) 380-7.
[41] G. Chatellier, E. Zapletal, D. Lemaitre, J. Menard, P. Degoulet, The number needed to treat: a clinically useful nomogram in its proper context, BMJ (Clinical research ed.) 312(7028) (1996) 426-9.
[42] J.A. Mauskopf, S.D. Sullivan, L. Annemans, J. Caro, C.D. Mullins, M. Nuijten, E. Orlewska, J. Watkins, P. Trueman, Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices--budget impact analysis, Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 10(5) (2007) 336-47.
[43] R.A. Willems, C.A. Bolman, I. Mesters, I.M. Kanera, A.A. Beaulen, L. Lechner, Cancer survivors in the first year after treatment: the prevalence and correlates of unmet needs in different domains, Psychooncology 25(1) (2016) 51-7.
[44] L. Thorsen, G.M. Gjerset, J.H. Loge, C.E. Kiserud, E. Skovlund, T. Flotten, S.D. Fossa, Cancer patients' needs for rehabilitation services, Acta oncologica (Stockholm, Sweden) 50(2) (2011) 212-22.
[45] A. Plass, U. Koch, Participation of oncological outpatients in psychosocial support, Psychooncology 10(6) (2001) 511-20.
[46] R. Luengo-Fernandez, J. Leal, A. Gray, R. Sullivan, Economic burden of cancer across the European Union: a population-based cost analysis, Lancet Oncol 14(12) (2013) 1165-74.
[47] B.F.M. Wijnen, I. Mosweu, M. Majoie, L. Ridsdale, R.J.A. de Kinderen, S. Evers, P. McCrone, A comparison of the responsiveness of EQ-5D-5L and the QOLIE-31P and mapping of QOLIE-31P to EQ-5D-5L in epilepsy, The European journal of health economics : HEPAC : health economics in prevention and care 19(6) (2018) 861-870.
[48] P. Bower, S. Gilbody, Stepped care in psychological therapies: access, effectiveness and efficiency. Narrative literature review, The British journal of psychiatry : the journal of mental science 186 (2005) 11-7.
[49] J.R. Bloom, S.L. Stewart, S. Chang, P.J. Banks, Then and now: quality of life of young breast cancer survivors, Psychooncology 13(3) (2004) 147-160.
[50] M.E. Schmidt, J. Wiskemann, K. Steindorf, Quality of life, problems, and needs of disease-free breast cancer survivors 5 years after diagnosis, Qual Life Res (2018).
[51] J. Howard-Anderson, P.A. Ganz, J.E. Bower, A.L. Stanton, Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review, J Natl Cancer Inst 104(5) (2012) 386-405.

[52] M. Krol, W. Brouwer, F. Rutten, Productivity costs in economic evaluations: past, present, future, PharmacoEconomics 31(7) (2013) 537-49.
[53] T.N.N.H. Institute, Guideline for conducting economic evaluations in healthcare. <https://english.zorginstituutnederland.nl/publications/reports/2016/06/16/guideline-for-economic-evaluations-in-healthcare>, 2016).
[54] M. Lidgren, N. Wilking, B. Jonsson, C. Rehnberg, Health related quality of life in different states of breast cancer, Qual Life Res 16(6) (2007) 1073-81.
[55] V.P. Retel, M.A. Joore, M. Knauer, S.C. Linn, M. Hauptmann, W.H. Harten, Cost-effectiveness of the 70-gene signature versus St. Gallen guidelines and Adjuvant Online for early breast cancer, Eur J Cancer 46(8) (2010) 1382-91.

**Appendix A.** Schematic representation of the model structure




**Abbreviations**

Costs associated with health states

cMenSympt: costs of group with menopausal symptoms

cRed: costs of group with a clinically significant reduction

cRecuccernce1st: costs of Breast Cancer recurrence in the first year

cRecuccernce2nd*: costs of Breast Cancer recurrence in the second year

cDeath: costs of death

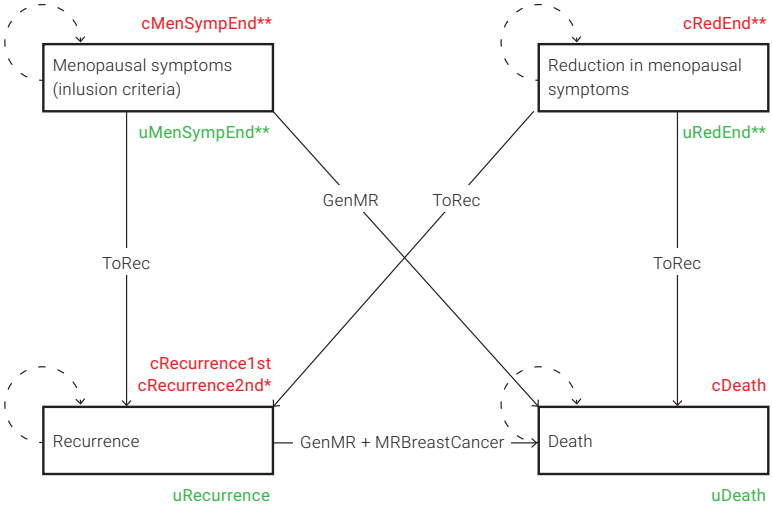
State change probabilities

pSympRedWithout: probability of a clinically significant reduction on FACT-ES for self-managed iCBT

pSympRedWith: probability of a clinically significant reduction on FACT-ES for guided iCBT

pSympRedWaitlist: probability of a clinically significant reduction on FACT-ES for waitlist control group

**From cycle 2 onwards**




ToRec: probability of going to recurrence
GenMR: general mortality rate
MRBreastCancer: mortality rate breast cancer

Utilities
uMenSymp: utility for health state menopausal symptoms
uRed: utility for health state reduction in menopausal symptoms
uRecurrence: utility associated with the health state recurrence
uDeath: utility of the health state

CHAPTER 6

# INTERNET-BASED COGNITIVE BEHAVIORAL THERAPY AIMED AT ALLEVIATING TREATMENT-INDUCED MENOPAUSAL SYMPTOMS IN BREAST CANCER SURVIVORS: MODERATORS AND MEDIATORS OF TREATMENT EFFECTS

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# ABSTRACT

## Purpose

Results from our recently conducted randomized controlled trial (RCT) indicated that Internet-based cognitive behavioral therapy (iCBT), with or without therapist support, is effective in reducing the perceived impact of hot flushes and night sweats (HF/NS) and overall levels of menopausal symptoms in breast cancer survivors with treatment-induced menopausal symptoms. The objective of this study was to identify potential moderators and mediators of these treatment effects.

## Methods

We used data of 235 women and compared the iCBT groups combined (n=156) with the control group (n=79). Bootstrapped multiple regression analyses with interaction terms (group x potential moderator) or indirect effects (mediation pathway) were conducted. Main outcome measures: Reductions in perceived impact of HF/NS and overall levels of menopausal symptoms.

## Results

Women with lower educational levels benefited most from the iCBT. Age, time since diagnosis, current endocrine treatment, oophorectomy, frequency of HF/NS, and psychological distress did not moderate the treatment effects. Factors that mediated treatment effects were the development of healthier beliefs about experiencing hot flushes in a social context, about the impact of night sweats on sleep and daily functioning, and about the ability to control and cope with hot flushes. The acquisition of behavioral coping strategies and decreased psychological distress did not mediate treatment effects.

## Conclusion

The results suggest that women with lower educational levels may benefit most from the current iCBT program, with or without therapist support. The development of healthier HF/NS beliefs contribute significantly to the observed positive effect of iCBT on menopausal symptom burden.

## INTRODUCTION

Many young breast cancer (BC) survivors are confronted with menopausal symptoms caused by their BC treatment [1]. The most prevalent and disruptive menopausal symptoms are hot flushes and night sweats (HF/NS) which negatively affect health-related quality of life (HRQOL), and can result in women discontinuing their endocrine treatment [2-5]. A cognitive behavioral therapy (CBT) program was developed by Hunter and colleagues to help women cope with these HF/NS [6, 7]. Four randomized controlled trials (RCTs) have provided evidence of the efficacy of this program, delivered in groups or in self-help or guided self-help format, in reducing the perceived impact of HF/NS in healthy women (MENOS2 trial, MENOS@work trial) [8, 9] and in BC survivors (MENOS1 trial and EVA trial) [10, 11]. To increase compliance in the Dutch setting [11] we translated the program into an Internet-based format [12]. We recently evaluated this Internet-based CBT program (iCBT) in an RCT and found that both guided and self-managed versions significantly improved the perceived impact of HF/NS, overall levels of menopausal symptoms, sleep quality, and the frequency of HF/NS when compared to a waiting list control group [13]. Moreover, the level of compliance was much higher compared to that observed in the earlier, group-based trial [11].

Because individuals may differ in their response to interventions, it is important to gain insight into characteristics that moderate treatment effects, and thus identify those who will benefit most from an intervention [14]. Two studies have investigated the potential moderators and mediators of the positive effects of the CBT program in the MENOS1 and 2 trials, Although Norton et al. [15] did not identify any demographic or psychosocial moderators in their study among healthy women with menopausal symptoms, Chilcot et al. [16] found that BC survivors who did not undergo chemotherapy, who had higher levels of psychological distress at baseline, and who were non-white benefited most from the CBT. Other studies have identified additional moderators of the effects of psychosocial interventions [17-19]. For example, a meta-analysis using individual cancer patient data from 22 RCTs found that younger patients and patients who had undergone chemotherapy and/or surgery benefited most from psychosocial interventions [17]. Results from two other RCTs evaluating the efficacy of CBT for chronic pain or iCBT for sleep problems reported that more highly educated patients benefited most from the interventions [18, 19].

Understanding the therapeutic change mechanisms responsible for treatment effects (i.e. mediators) provides valuable information for theory testing and further refinement of an intervention [14]. The proposed change mechanisms of our iCBT for women with menopausal symptoms reflect the general change mechanisms of CBT, i.e. changing maladaptive beliefs (cognitions) and behaviors. More specifically, our iCBT program targets three types of negative beliefs: the belief that hot flushes are embarrassing and that others will judge you when you experience hot flushes in a social context, the belief that you cannot influence the extent to which night sweats impact negatively on sleep and daily functioning and the belief that you are unable to cope or control hot flushes [20]. Additionally, the iCBT teaches two behavioral strategies: 1) ways to accept, ignore and/or use humor to cope with hot flushes (positive coping behavior) and 2) ways to remain in social situations even in the presence of HF/NS (avoidance behavior) [21, 22]. The iCBT also aims to reduce psychological distress, as psychological distress negatively affects the perception and the frequency of hot flushes [22]. Chilcot et al. [16] found that, among BC survivors, changing all three unhelpful beliefs about HF/NS, improving sleep, and decreasing psychological distress mediated the treatment effects of CBT on HF/NS. Norton and colleagues [15] replicated these findings, in part, reporting that changes in beliefs about coping and control over hot flushes, and about the impact of night sweats on sleep and daily functioning, mediated improvements in HF/NS following CBT. In both studies, the beliefs that one is able to control and cope effectively with hot flushes was identified as the main mediator of the treatment effects [15, 16].

The objective of the current study was to determine which of the hypothesized variables actually moderate and mediate the effects of our iCBT program among BC survivors who have experienced treatment-induced menopausal symptoms.

## METHODS

### Research design and study sample

A detailed description of the design of the RCT has been reported elsewhere [23]. Briefly, from 2015 to 2017, we conducted an RCT to evaluate the efficacy of iCBT, with and without therapist support, in reducing treatment-induced menopausal symptom burden in BC survivors. Patients were

recruited from 12 hospitals in the Netherlands. Following provision of the informed consent and completion of a baseline questionnaire (T0), 254 patients were randomized to guided iCBT, self-managed iCBT, or a waiting list (control group).

Women randomized to either of the two interventions had access to a six-week iCBT program. A strong emphasis was placed on HF/NS, but other related problems were also addressed (e.g. sleep, stress). The level of literacy for the program was set at B1, making it comprehensible for at least 80% of the population [24]. Women in the guided iCBT group received an additional telephone intake and weekly online feedback from a therapist. Participants allocated to the control group received usual care, which did not involve any form of care aimed at coping with menopausal symptoms.

Follow-up assessments were at 10 weeks (short-term, T1) and 24 weeks post-randomization (longer-term, T2). All institutional review boards of the participating centers approved the study. Data from 235 women (156 in the intervention groups and 79 patients in the control group) who completed all assessments were used for the current analysis.

## Measures

Patient sociodemographic and clinical characteristics were assessed at baseline and included, among others, age, educational level and type of BC treatment.



### *Outcome variables*

The perceived impact of HF/NS was assessed by the problem rating subscale of the Hot Flush Rating Scale (HFRS [25]). Additionally, the overall levels of menopausal symptoms was assessed with the Functional Assessment of Cancer Treatment-Endocrine Symptoms questionnaire (FACT-ES [26]).

### *Potential moderators*

The choice of potential moderators was based on, but not limited to previous literature [15-19] and included age, education, time since diagnosis, current endocrine treatment, past oophorectomy, baseline frequency of hot flushes and night sweats as assessed by the HFRS frequency subscales [25], and baseline levels of psychological distress as assessed by the Hospital Anxiety and Depression Scale (HADS [27]).

### *Potential mediators*

The choice of potential mediators was based on the cognitive model of Hunter et al. and related studies [15, 16, 22]. The HF/NS Beliefs and Behavior Scale – Short Form was used to assess HF/NS beliefs and behaviors, organized into three belief subscales and two behavior subscales. It includes items from the Hot Flush Beliefs Scale [20] and the Hot Flush Behavior Scale [21] and is included in a Supplementary File. Psychological distress was assessed with the HADS [27].

## Statistical analyses

Scale scores were calculated according to published scoring algorithms. Missing values were replaced by the average score of the completed items if at least 50% of the items in that scale were completed. Since the observed differences in the efficacy of the guided and self-managed iCBT groups were relatively small, and to increase statistical power, these groups were combined for the analyses [13].

We used the PROCESS Macro developed by Hayes [28] to conduct path analyses in which ordinary least squares regression-based models are constructed. A bootstrapping method was used to calculate 99% confidence intervals of the conditional effect in the moderation model and the indirect effect in the mediation model.

For the moderation analyses, a regression-based model was constructed for each potential moderator separately in order to estimate the conditional (interaction) effect. Each model included the change score (T0 - T2) for perceived impact of HF/NS or for overall levels of menopausal symptoms as the dependent variable, the main effects of group (intervention versus control) and moderator, and a group by moderator interaction effect. Variables that significantly moderated the relationship between group allocation and change in perceived impact of HF/NS or overall levels of menopausal symptoms were adjusted for in the mediation analysis.

Prior to the mediation analysis, we used Student's t-tests to examine whether changes between baseline to short-term follow-up (T0 - T1) in HF/NS beliefs and behaviors and psychological distress were significantly different between the intervention and the control group. Subsequently, regression-based models were constructed to estimate the indirect effect of each potential mediator separately. Each model included the change score (T0 - T2) of perceived impact of HF/NS or overall levels of menopausal symptoms as the dependent variable, the change score between T0 - T1

of the potential mediator and group. We calculated partially standardized effects, which express the indirect effect relative to the standard deviation of the dependent variable [28]. All analyses were conducted in SPSS version 22.

# RESULTS

## Sample characteristics

Sociodemographic, clinical and menopause-related characteristics of the study sample are shown in Table 1. The mean age of the women was 47.5 years (standard deviation (SD) = 5.4) and 45.5% had completed college or university. The average time since BC diagnosis was 3.1 years (SD = 1.4) and the majority had received chemotherapy (94%) and was still undergoing endocrine treatment (82%). At baseline, women experienced, on average, 50.2 hot flushes (SD = 39.0) and 18.1 night sweats (SD = 13.4) per week. The mean baseline problem rating score was 4.9 (SD = 1.9) for HF/NS, and 50.7 (SD = 8.7) for overall levels of menopausal symptoms. All baseline characteristics were balanced across groups.

## Moderation analyses

Results of the interaction analyses are shown in Table 2. Only educational level significantly moderated the relationship between group allocation and changes in perceived impact of HF/NS ((interaction effect (estimate) = 1.38, 99% CI = 0.05–2.71)). That is, patients who completed secondary or vocational education showed a significantly greater decrease in perceived impact of HF/NS (unstandardized regression coefficient (*B* = -1.49, 99% CI = -2.39– -0.59) compared to women who completed college or university (*B* = -0.11, 99% CI = -1.10–0.84) (See Figure 1). We did not observe any moderating effects of age, time since diagnosis, current endocrine treatment, past oophorectomy, frequency of hot flushes or night sweats, and psychological distress.

**Table 1.** Sociodemographic, clinical and menopause-related characteristics

| | All patients (n = 235) | | iCBT patients* (n = 156) | | Control patients (n = 79) | |
|---|---|---|---|---|---|---|
| Age, *mean years (SD)* | 47.50 | (5.36) | 47.70 | (5.24) | 47.02 | (5.61) |
| Education, *n (%)* | | | | | | |
| High school & vocational education | 128 | (54.5%) | 85 | (54.5%) | 43 | (54.4%) |
| College/university | 107 | (45.5%) | 71 | (45.5%) | 36 | (45.6%) |
| Time since diagnosis, *mean years (SD)* | 3.10 | (1.39) | 3.13 | (1.42) | 3.04 | (1.35) |
| Chemotherapy | | | | | | |
| Endocrine therapy: current use, *n (%)* | 193 | (82.1%) | 128 | (82.1%) | 65 | (82.3%) |
| Oophorectomy, *n (%)* | 43 | (18.3%) | 28 | (17.9%) | 15 | (19.0%) |
| Chemotherapy, *n (%)* | 221 | (94.0) | 148 | (94.9) | 73 | (92.4) |
| Prescribed medication for HF/NS | 26 | (11.1) | 15 | ( 9.6) | 11 | (13.9) |
| Hot flush frequency per week, *mean (SD)* | 50.22 | (39.02) | 51.78 | (40.33) | 47.14 | (36.36) |
| Night sweats frequency per week, *mean (SD)* | 18.07 | (13.38) | 18.02 | (13.02) | 18.16 | (14.15) |
| Perceived impact of HF/NS, *mean (SD)*† | 4.87 | (1.86) | 4.97 | (1.81) | 4.67 | (1.94) |
| Overall levels of menopausal symptoms, *mean (SD)*†† | 50.67 | (8.72) | 50.96 | (9.01) | 50.12 | (8.15) |

Abbreviations: iCBT, Internet-based cognitive behavioral therapy; n, number; SD, standard deviation.
* 'iCBT patients' include all women allocated to the guided or self-managed iCBT group.
† Score range: 0 – 10, with higher scores reflecting a higher perceived impact of HF/NS.
†† Score range: 0 – 72, with higher scores reflecting lower overall levels of menopausal symptoms.

**Table 2.** Interaction effects of potential moderator variables with treatment group on longer-term follow-up changes in perceived impact of HF/NS (HFRS problem rating scale) and overall levels of menopausal symptoms (FACT-ES)

| | Perceived impact of HF/NS | | | Overall levels of menopausal symptoms | | |
|---|---|---|---|---|---|---|
| **Potential Moderator** | **Estimate** | **(99% CI)** | **p** | **Estimate** | **(99% CI)** | **p** |
| Age | -0.06 | (-0.18 – 0.07) | .22 | 0.22 | (-0.23 – 0.67) | .20 |
| Educational level (high school/ vocational* vs college/ university) | 1.38 | ( 0.05 – 2.71) | **<.01** | -4.84 | (-9.74 – 0.06) | .01 |
| Time since diagnosis (<3 years* vs ≥3 years) | 0.14 | (-1.21 – 1.49) | .79 | 1.69 | (-3.23 – 6.61) | .37 |
| Current endocrine treatment (no* vs yes) | -0.16 | (-1.92 – 1.60) | .82 | 1.23 | (-2.75 – 5.20) | .54 |
| Oophorectomy (no* vs yes) | 0.17 | (-1.57 – 1.90) | .80 | -0.63 | (-7.01 – 5.76) | .80 |
| Hot flush frequency | 0.01 | (-0.02 – 0.02) | .44 | -0.01 | (-0.07 – 0.06) | .75 |
| Night sweats frequency | -0.03 | (-0.08 – 0.02) | .10 | 0.15 | (0.02 – 0.33) | .03 |
| Psychological distress | 0 | (-0.11 – 0.10) | .95 | 0.12 | (-0.25 – 0.50) | .40 |

Note: Bold font indicates significant moderation effect at p < .01.
Abbreviations: CI, confidence interval; FACT-ES, Functional Assessment of Cancer Treatment- Endocrine symptoms; HF/NS, hot flushes / night sweats; HFRS, Hot Flush Rating Scale.
* indicates reference category.



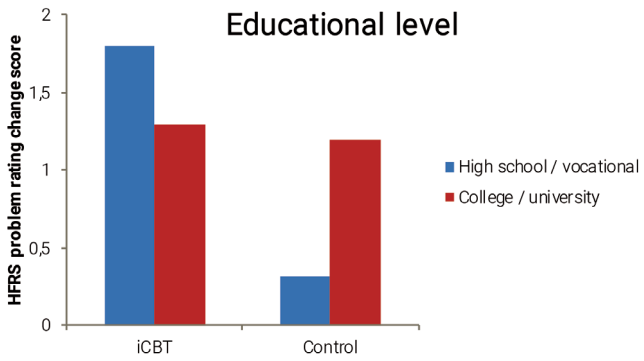


**Figure 1.** Improvements from baseline to longer-term follow-up in perceived impact of Hot flushes / night sweats (HFRS problem rating scale), stratified by educational level.
Abbreviations: HFRS, Hot Flush Rating Scale.

## Mediation analyses

Patients in the iCBT groups reported significantly greater improvement (T0 - T1) on all three belief scales, i.e. beliefs about hot flushes in a social context (mean difference = 0.35, 99% CI = 0.02–0.67), beliefs about night sweats and sleep (mean difference = 0.38, 99% CI = 0.02–0.73), and beliefs about coping/control (mean difference = -0.54, 99% CI = -0.87– -0.22) compared to the control group. Patients allocated to the iCBT groups also reported significantly greater improvement (T0 - T1) in effective coping behavior (mean difference = 0.45, 99% CI = -0.76– -0.14) as compared to the control group (Table 3). No significant group differences were observed for avoidance behavior or psychological distress.

Results from the mediation analyses (Table 4) indicated that changes in beliefs about hot flushes in a social context and beliefs about coping/control significantly mediated the relationship between group allocation and changes in perceived impact of HF/NS ((partially standardized indirect effect (estimate) = 0.10, 99% CI = 0.01–0.24; estimate = 0.19, 99% CI = 0.07–0.39, respectively)) and between group allocation and changes in menopausal symptoms (estimate = 0.07, 99% CI = 0.00–0.19; estimate = 0.17, 99% CI = 0.04–0.35, respectively). This indicates that the development of healthier beliefs about hot flushes in a social context and beliefs about one's ability to control and cope effectively with hot flushes contribute to lower perceived impact of HF/NS and reduced menopausal symptom burden in the iCBT groups. Beliefs about coping/control had the largest mediating effect in the individual mediation models. That is, improvement in beliefs about one's ability to cope effectively with hot flushes accounted for the largest percentage (43%) of the total treatment effect for perceived impact of HF/NS and overall levels of menopausal symptoms.

We found that changes in beliefs about night sweats and sleep also mediated the relationship between group allocation and changes in perceived impact of HF/NS (estimate = 0.09, 99% CI = -0.21– -0.01), indicating that the development of healthier beliefs about one's ability to reduce the impact of night sweats on sleep and daily functioning contribute to a lower perceived impact of HF/NS in the iCBT groups. We did not find any mediating effects of changes in positive coping behavior, avoidance behavior, or psychological distress.

We conducted additional analyses correcting for potential confounding effects of educational level. These analyses did not alter the results as reported above (data not shown).

**Table 3.** Between-group changes in mean change from baseline and short-term follow -up scores on potential mediators of treatment effects

| | T0 | | | T1 | | | Between-group difference T0-T1 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Potential mediator** | **N** | **Mean** | **(SD)** | **N** | **Mean** | **(SD)** | **Mean change** | **(SE)** | **p** |
| **Beliefs about hot flushes in a social context†** | | | | | | | | | |
| All intervention patients | 156 | 1.91 | (1.18) | 154 | 1.21 | (1.12) | 0.35 | (0.13) | **<.01** |
| Control group | 79 | 1.84 | (1.27) | 79 | 1.49 | (1.19) | | | |
| **Beliefs about night sweats and sleep†** | | | | | | | | | |
| All intervention patients | 156 | 1.09 | (1.09) | 154 | 1.70 | (1.03) | 0.38 | (0.12) | **<.01** |
| Control group | 78 | 1.06 | (1.06) | 79 | 2.01 | (0.99) | | | |
| **Beliefs about coping/control*** | | | | | | | | | |
| All intervention patients | 156 | 3.02 | (0.97) | 154 | 3.81 | (0.86) | -0.54 | (0.13) | **<.001** |
| Control group | 79 | 3.14 | (1.08) | 79 | 3.38 | (0.95) | | | |
| **Positive coping behavior*** | | | | | | | | | |
| All intervention patients | 156 | 3.42 | (0.94) | 153 | 3.89 | (0.73) | -0.45 | (0.11) | **<.001** |
| Control group | 79 | 3.60 | (0.86) | 79 | 3.62 | (0.84) | | | |
| **Avoidance behavior†** | | | | | | | | | |
| All intervention patients | 156 | .79 | (0.89) | 153 | .59 | (0.84) | 0.17 | (0.10) | .08 |
| Control group | 79 | .79 | (0.89) | 79 | .76 | (0.97) | | | |
| **Psychological distress‡** | | | | | | | | | |
| All intervention patients | 156 | 11.16 | (6.94) | 156 | 6.39 | (0.52) | 1.00 | (0.63) | .11 |
| Control group | 79 | 11.17 | (6.43) | 79 | 6.50 | (0.73) | | | |

Note: bold font indicates significant between group differences at p < .01.
Abbreviations: N, number; SD, standard deviation, SE, standard error; T0, baseline assessment; T1, short-term follow-up assessment.
† scale range: 0 – 5, higher scores reflect more negative beliefs and behaviors.
* scale range: 0 – 5, higher scores reflect more positive beliefs and behaviors.
‡ scale range: 0 – 42, higher scores reflect more psychological distress.

**Table 4.** Indirect effects of potential mediators of treatment effects on baseline to longer-term follow-up changes in perceived impact of HF/NS (HFRS problem rating scale) and overall levels of menopausal symptoms (FACT-ES)

| | Perceived impact of HF/NS | | | Overall levels of menopausal symptoms | | |
|---|---|---|---|---|---|---|
| | **Estimate** | **(99% CI)** | **% of total effect explained by mediator** | **Estimate** | **(99% CI)** | **% of total effect explained by mediator** |
| **Total treatment effect#** | | | | | | |
| | -0.85 | (0.34 – 1.37) | | 2.73 | (0.26 – 5.20) | |
| **Indirect effect of treatment through beliefs and behaviors†** | | | | | | |
| Beliefs about hot flushes in a social context | -0.10 | **(-0.23 – -0.01)** | 22.7 | 0.07 | **(0.00 – 0.19)** | 18.5 |
| Beliefs about night sweats and sleep | -0.09 | **(-0.21 – -0.01)** | 19.0 | 0.05 | (-0.02 – 0.17) | 13.0 |
| Beliefs about coping/control | -0.19 | **(-0.37 – -0.06)** | 43.1 | 0.17 | **(0.06 – 0.34)** | 42.5 |
| Positive coping behavior | -0.06 | (-0.20 – 0.04) | 14.3 | 0.08 | (-0.01 – 0.21) | 21.7 |
| Avoidance behavior | -0.01 | (-0.07 – 0.06) | 1.3 | 0.01 | (-0.04 – 0.08) | 3.6 |
| Psychological distress | -0.02 | (-0.10 – 0.01) | 5.1 | 0.05 | (-0.03 – 0.16) | 12.7 |

Note: Bold font indicates significant mediation effects at $p < .01$.
Abbreviations: CI, confidence interval; FACT-ES, Functional Assessment of Cancer Therapy - Endocrine Symptoms; HF/NS, hot flushes/night sweats; HFRS, Hot Flush Rating Scale.
# Unstandardized estimate for treatment effect, unadjusted for mediators.
† Partially standardized estimates of the indirect effect of treatment (intervention versus control) on the perceived impact of HF/NS and overall levels of menopausal symptoms through the mediator.

## DISCUSSION

The aim of the current study was to identify patient characteristics that moderate, and therapeutic change mechanisms that mediate the beneficial effects of iCBT on treatment-induced menopausal symptoms in BC survivors [13]. Our results indicate that women with a high school or vocational training degree in the iCBT group improved more in perceived

impact of HF/NS than their counterparts in the control group, whereas this was not the case for women with a college or university degree. Women with a higher educational level in the control group improved to almost the same extent as their counterparts in the intervention group. This contrasts with findings from previous studies that either reported no moderating effect of education or the opposite effect (i.e. more highly educated women benefiting most) [15-19]. A possible explanation for our finding is that more highly educated women who were allocated to the control group may have sought alternative sources of information or strategies for dealing with their menopausal symptoms, whereas the less well educated women in the control group may have been less likely to do so [29]. Another possibility is that our iCBT program was designed to be understandable for women with all levels of education, and thus the language used in the iCBT was quite basic. It may be that more highly educated women could have benefited from a more sophisticated approach to the provision of information and behavioral strategies. This suggests that a more tailored version of the program that takes the educational level of participants into consideration may be more effective [29]. Although Chilcot et al. reported that baseline psychological distress moderated the effect of CBT on HF/NS, Norton et al. did not observe such an effect [15, 16]. This was also the case in our study. The fact that we did not observe a moderating effect of baseline psychological distress may be due to the fact that the women who participated in our study reported low levels of distress at baseline.

In line with the MENOS trials, the iCBT resulted in healthier HF/NS beliefs and behaviors [15, 16]. Our findings indicate that changes in beliefs about feelings of embarrassment or feeling judged by others when experiencing hot flushes in a social context, beliefs about one's ability to influence the extent to which night sweats negatively impact sleep and daily functioning, and beliefs about one's ability to control and cope effectively with hot flushes mediated the positive effect observed on the perceived impact of HF/NS. The development of healthier beliefs about experiencing hot flushes in a social context and beliefs about one's ability to cope effectively with hot flushes also contributed to the positive intervention effect found on overall menopausal symptom burden as assessed by the FACT-ES. This suggests that, although our iCBT program was primarily targeted at the development of healthier beliefs and behaviors in relation to HF/NS, the changes in the beliefs also had a salutary effect on a broader range of menopausal symptoms.

Although, a positive trend was observed, changes in psychological distress were not found to significantly mediate the observed positive effects of the iCBT program on the perceived impact of HF/NS or overall menopausal symptoms. The MENOS trials yielded mixed findings [15, 16]. In our study, the decrease in distress was very similar between the intervention and control groups. This decrease in distress was anticipated in the intervention groups, but not in the control group. We would note that, for all groups, both baseline and follow-up distress scores were in the normal range. This reflects the fact that we excluded women from the study who were judged as being highly distressed during the screening interview. In line with previous studies, we did not find a significant mediating effect of positive coping behaviors [15, 16]. However, a positive trend suggests that the development of a healthier coping style could have contributed to the treatment effects. Although the iCBT program had a positive effect on both coping beliefs and behavior, it appears that the primary mediating effect was via the beliefs about being able to cope with HF/NS. These findings also suggest that, in contact with patients, healthcare professionals should stress that the impact of HF/NS can be influenced and should inform women about effective coping strategies.

Although the study of Chilcot et al. [16] reported that sleep mediated the effect of CBT on the perceived impact of HF/NS, we chose not to include sleep in our analyses because we considered the causal directionality to be questionable. That is, it is just as plausible, or even more plausible that improving the experience of night sweats has a positive impact on sleep than vice versa.

Several limitations of the current study should be noted. First, the sample size was not specifically powered to detect small effects. We endorse recommendations that have been made to conduct meta-analyses based on individualized patient data (IPD) derived from several RCTs in order to increase power and replicate previous findings [17, 30]. Second, although we believe we have included the most important potential moderating and mediating variables, we do not presume to have been exhaustive. For example, our study was not suitable for replicating the moderating effect of chemotherapy as observed by Chilcot and colleagues [16], since 94% of the women in our sample had received chemotherapy. This study also had several notable strengths. This included the RCT design, multicenter participation and the high questionnaire completion rate.

In conclusion, our findings indicate that BC survivors with a high school/vocational training degree benefited most from the iCBT program for treatment-induced HF/NS, and that the positive effects of the iCBT program on the perceived impact of HF/NS and overall menopausal symptom burden were mediated by the development of healthier HF/NS beliefs. This suggests that the iCBT program should be tailored to the educational level of women, and that more effort be devoted to strengthening the behavioral component of the program.

## REFERENCES


[1] N.E. Avis, S. Crawford, J. Manuel, Psychosocial problems among younger women with breast cancer, Psychooncology 13(5) (2004) 295-308.

[2] J.S. Carpenter, M.A. Andrykowski, Menopausal symptoms in breast cancer survivors., Oncol Nurs Forum 26(8) (1999) 1311-1317.

[3] P. Gupta, D.W. Sturdee, S.L. Palin, K. Majumder, R. Fear, T. Marshall, I. Paterson, Menopausal symptoms in women treated for breast cancer: the prevalence and severity of symptoms and their perceived effects on quality of life, Climacteric 9(1) (2006) 49-58.

[4] Z. Moon, M.S. Hunter, R. Moss-Morris, L.D. Hughes, Factors related to the experience of menopausal symptoms in women prescribed tamoxifen, J Psychosom Obstet Gynaecol (2016) 1-10.

[5] C.C. Murphy, L.K. Bartholomew, M.Y. Carpentier, S.M. Bluethmann, S.W. Vernon, Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review, Breast Cancer Res Treat 134(2) (2012) 459-78.

[6] M.S. Hunter, K.L.M. Liao, Evaluation of a four-session cognitive-behavioural intervention for menopausal hot flushes, Br. J. Health Psychol. 1 (1996) 113-125.

[7] M.S. Hunter, S. Coventry, H. Hamed, I. Fentiman, E.A. Grunfeld, Evaluation of a group cognitive behavioural intervention for women suffering from menopausal symptoms following breast cancer treatment, Psychooncology 18(5) (2009) 560-3.

[8] B. Ayers, M. Smith, J. Hellier, E. Mann, M.S. Hunter, Effectiveness of group and self-help cognitive behavior therapy in reducing problematic menopausal hot flushes and night sweats (MENOS 2): a randomized controlled trial, Menopause 19(7) (2012) 749-759.

[9] C. Hardy, A. Griffiths, S. Norton, M.S. Hunter, Self-help cognitive behavior therapy for working women with problematic hot flushes and night sweats (MENOS@ Work): a multicenter randomized controlled trial, Menopause 25(5) (2018) 508-519.

[10] E. Mann, M.J. Smith, J. Hellier, J.A. Balabanovic, H. Hamed, E.A. Grunfeld, M.S. Hunter, Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial, Lancet Oncol 13(3) (2012) 309-318.

[11] S.F.A. Duijts, M. Van Beurden, H.S.A. Oldenburg, M.S. Hunter, J.M. Kieffer, M.M. Stuiver, M.A. Gerritsma, M.B.E. Menke-Pluymers, P.W. Plaisir, H. Rijna, A.M.F. Lopes Cardozo, G.J. Timmers, S. Van der Meij, H. Van der Veen, N. Bijker, L.M. De Widt-Levert, M.M. Geenen, G. Heuff, E.J. Van Dulken, E. Boven, N.K. Aaronson, Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: Results of a randomized controlled multicenter trial., Journal of Clinical Oncology 30(33) (2012) 4124-4133.

[12] V. Atema, M. van Leeuwen, H.S.A. Oldenburg, M. van Beurden, M.S. Hunter, N.K. Aaronson, An Internet-based cognitive behavioral therapy for treatment-induced menopausal symptoms in breast cancer survivors: results of a pilot study, Menopause 24(7) (2017) 762-767.
[13] V. Atema, M. van Leeuwen, J.M. Kieffer, H.S.A. Oldenburg, M. van Beurden, M.A. Gerritsma, M.A. Kuenen, P.W. Plaisier, A.M.F. Lopes Cardozo, Y.E.A. van Riet, G. Heuff, H. Rijna, S. van der Meij, E.M. Noorda, G.J. Timmers, B.C. Vrouenraets, M. Bollen, H. van der Veen, N. Bijker, M.S. Hunter, N.K. Aaronson, Efficacy of Internet-Based Cognitive Behavioral Therapy for Treatment-Induced Menopausal Symptoms in Breast Cancer Survivors: Results of a Randomized Controlled Trial, J Clin Oncol 37(10) (2019) 809-22.
[14] H.C. Kraemer, G.T. Wilson, C.G. Fairburn, W.S. Agras, Mediators and moderators of treatment effects in randomized clinical trials, Archives of general psychiatry 59(10) (2002) 877-83.
[15] S. Norton, J. Chilcot, M.S. Hunter, Cognitive-behavior therapy for menopausal symptoms (hot flushes and night sweats): moderators and mediators of treatment effects, Menopause-J. N. Am. Menopause Soc. 21(6) (2014) 574-578.
[16] J. Chilcot, S. Norton, M.S. Hunter, Cognitive behaviour therapy for menopausal symptoms following breast cancer treatment: Who benefits and how does it work?, Maturitas 78(1) (2014) 56-61.
[17] J. Kalter, I.M. Verdonck-de Leeuw, M.G. Sweegers, N.K. Aaronson, P.B. Jacobsen, R.U. Newton, K.S. Courneya, J.F. Aitken, J. Armes, C. Arving, L.J. Boersma, A.M.J. Braamse, Y. Brandberg, S.K. Chambers, J. Dekker, K. Ell, R.J. Ferguson, M.F.M. Gielissen, B. Glimelius, M.M. Goedendorp, K.D. Graves, S.P. Heiney, R. Horne, M.S. Hunter, B. Johansson, M.L. Kimman, H. Knoop, K. Meneses, L.L. Northouse, H.S. Oldenburg, J.B. Prins, J. Savard, M. van Beurden, S.W. van den Berg, J. Brug, L.M. Buffart, Effects and moderators of psychosocial interventions on quality of life, and emotional and social function in patients with cancer: An individual patient data meta-analysis of 22 RCTs, Psychooncology 27(4) (2018) 1150-1161.
[18] J.E. Broderick, F.J. Keefe, S. Schneider, D.U. Junghaenel, P. Bruckenthal, J.E. Schwartz, A.T. Kaell, D.S. Caldwell, D. McKee, E. Gould, Cognitive behavioral therapy for chronic pain is effective, but for whom?, Pain 157(9) (2016) 2115-23.
[19] N. Vincent, K. Walsh, S. Lewycky, Determinants of success for computerized cognitive behavior therapy: examination of an insomnia program, Behavioral sleep medicine 11(5) (2013) 328-42.
[20] M.J. Rendall, L.M. Simonds, M.S. Hunter, The Hot Flush Beliefs Scale: a tool for assessing thoughts and beliefs associated with the experience of menopausal hot flushes and night sweats, Maturitas 60(2) (2008) 158-169.
[21] M.S. Hunter, B. Ayers, M. Smith, The Hot Flush Behavior Scale: a measure of behavioral reactions to menopausal hot flushes and night sweats, Menopause 18(11) (2011) 1178-1183.
[22] M.S. Hunter, E. Mann, A cognitive model of menopausal hot flushes and night sweats, J Psychosom Res 69(5) (2010) 491-501.

[23] V. Atema, M. van Leeuwen, H.S. Oldenburg, V. Retel, M. van Beurden, M.S. Hunter, N.K. Aaronson, Design of a randomized controlled trial of Internet-based cognitive behavioral therapy for treatment-induced menopausal symptoms in breast cancer survivors, BMC Cancer 16(1) (2016) 920.
[24] Common European Framework of reference for languages: learning, teaching, assessment. <https://rm.coe.int/cefr-companion-volume-with-new-descriptors-2018/1680787989>, 2018).
[25] M.S. Hunter, K.L.M. Liao, A psychological analysis of menopausal hot flushes, Br. J. Clin. Psychol. 34 (1995) 589-599.
[26] L.J. Fallowfield, S.K. Leaity, A. Howell, S. Benson, D. Cella, Assessment of quality of life in women undergoing hormonal therapy for breast cancer: validation of an endocrine symptom subscale for the FACT-B, Breast Cancer Res Treat 55(2) (1999) 189-199.
[27] A.S. Zigmond, R.P. Snaith, The hospital anxiety and depression scale, Acta Psychiatr Scand 67(6) (1983) 361-370.
[28] A.F. Hayes, Introduction to Mediation, Moderation, and Conditional Process Analysis; A regression-Based Approach, The Guilford Press, New York, 2018.
[29] D.R. Longo, Understanding health information, communication, and information seeking of patients and consumers: a comprehensive and integrated model, Health expectations : an international journal of public participation in health care and health policy 8(3) (2005) 189-94.
[30] R.D. Riley, P.C. Lambert, G. Abo-Zaid, Meta-analysis of individual participant data: rationale, conduct, and reporting, BMJ (Clinical research ed.) 340 (2010) c221.

## SUPPLEMENTARY FILE

The Short Form HFBBS is a 16 item scale that includes items from the Hot Flush Beliefs Scale (Rendall et al 2008) and the Hot Flush Behaviour Scale (Hunter et al 2011), and offers a shorter instrument with similar psychometric properties.

140 women with hot flushes (baseline data from Ayers et al 2012) completed both scales and principal component factor analyses performed to examine relationships between items and factor loadings. In the original Hot flush Beliefs Scale paper (Rendall et al 2008) several items were rather repetitive. Those loading less strongly on each factor were removed. The two scales were originally developed to assess hot flush beliefs and behaviours to be used in evaluation of cognitive behavioural interventions. In mediation analyses of CBT in two trials, some subscales were shown to mediate and or change following CBT, while another did not; consequently in the short form a subscale was removed, i.e. cooling or safety behaviours.

The short form scale is shown above and includes 10 belief items and 6 behaviour items, assessing five subscales:

| | | Items | Cronbach alpha |
|---|---|---|---|
| Beliefs: | 1. HF in Social Context | 4,5,6,9 | 0.90 |
| | 2. Beliefs about night sweats and sleep | 2,3,10 | 0.73 |
| | 3. Beliefs about coping/control | 1,7,8. | 0.78 |
| Behaviours: | 4. Positive coping behaviours | 11,13,14 | 0.60 |
| | 5. Avoidance behaviour | 12,15,16. | 0.76 |

To create subscale scores items 1, 3 and 8 are reversed. Items are then scored 0-5, and added together according to subscales (above) and divided by the number of items in the subscale. For subscales 1, 2, 3 and 5 a higher score reflects more negative beliefs/behaviours and for 4 a higher score reflects positive behaviours. Internal reliability (Cronbach alpha coefficients) is shown above with coefficients from the original studies in brackets. The short form subscales correlate above 0.90 with the original longer subscales and have similar relationships with hot flush Frequency and Problem-rating.

This questionnaire lists beliefs about hot flushes and night sweats and reactions to them. Please circle the response that best describes how much you agree or disagree with each statement based on your beliefs and reactions to your flushes and sweats in the past two weeks. There are no right or wrong answers.

| | | Strongly Disagree | Moderately disagree | Mildly disagree | Mildly agree | Moderately agree | Strongly agree |
|---|---|---|---|---|---|---|---|
| **1** | I am able to cope with the physical discomfort of hot flushes | 0 | 1 | 2 | 3 | 4 | 5 |
| **2** | When I have night sweats, I won't be able to get back to sleep | 0 | 1 | 2 | 3 | 4 | 5 |
| **3** | If I'm woken up with sweats, I can manage the next day | 0 | 1 | 2 | 3 | 4 | 5 |
| **4** | When I have a hot flush, I am embarrassed | 0 | 1 | 2 | 3 | 4 | 5 |
| **5** | When I have a hot flush, I am anxious about how I look | 0 | 1 | 2 | 3 | 4 | 5 |
| **6** | When I have a hot flush, other people will think I am incompetent | 0 | 1 | 2 | 3 | 4 | 5 |
| **7** | I feel overwhelmed by my hot flushes | 0 | 1 | 2 | 3 | 4 | 5 |
| **8** | I am coping effectively with my hot flushes | 0 | 1 | 2 | 3 | 4 | 5 |
| **9** | Having hot flushes makes me more concerned with what other people think about me | 0 | 1 | 2 | 3 | 4 | 5 |
| **10** | When I have night sweats, it is harder to cope the next day | 0 | 1 | 2 | 3 | 4 | 5 |
| **11** | When I have hot flushes I carry on and ignore them | 0 | 1 | 2 | 3 | 4 | 5 |
| **12** | I have to leave or avoid some social situations because of hot flushes | 0 | 1 | 2 | 3 | 4 | 5 |
| **13** | When I have hot flushes or night sweats I try to accept them and let them flow over me | 0 | 1 | 2 | 3 | 4 | 5 |
| **14** | I use humour to deal with hot flushes | 0 | 1 | 2 | 3 | 4 | 5 |
| **15** | I don't go out as much now because of hot flushes | 0 | 1 | 2 | 3 | 4 | 5 |
| **16** | I don't use public transport because I have hot flushes | 0 | 1 | 2 | 3 | 4 | 5 |

## REFERENCES

Rendall MJ, Simmons LM & Hunter MS. The Hot Flush beliefs Scale: a tool for assessing thoughts and beliefs associated with experience of menopausal hot flushes and night sweats. *Maturitas,* 2008; 60: 158-169.

Hunter MS, Ayers B, Smith M. The Hot Flush Behavior Scale: a measure of behavioral reactions to menopausal hot flushes and night sweats. *Menopause: The Journal of the North American Menopause Society*. 2011;18 11; 1178-83.

Ayers B, Smith M, Hellier J, Mann E and Hunter MS. Effectiveness of group and self-help cognitive behaviour therapy to reduce problematic menopausal hot flushes and night sweats (MENOS 2): a randomized controlled trial. *Menopause* 2012;19,7:749-759.

Norton S, Chilcot J, Hunter MS. Cognitive behaviour therapy for menopausal symptoms (hot flushes and night sweats): moderators and mediators of treatment effects. *Menopause* 2014; 21: 6, 574–578.

Chilcot J, Norton S, Hunter MS. Cognitive behaviour therapy for menopausal symptoms following breast cancer treatment: who benefits and how does it work? *Maturitas* 2014; 78: 1; 56 – 61.

CHAPTER 7

# GENERAL DISCUSSION

In the previous chapters of this thesis we have described outcomes from our pilot-study and large scale randomized controlled trial (RCT) evaluating the efficacy of iCBT, with or without therapist support, in alleviating treatment-induced menopausal symptom burden in BC survivors. We provided information about the feasibility of the iCBT program, the efficacy, and cost-effectiveness of the iCBT program, and described patients' characteristics that moderate and therapeutic change mechanisms that mediate the observed treatment effects. In this chapter, we will: a] summarize the main findings of our trial, b] discuss methodological considerations and c] reflect upon research and clinical implications.

## MAIN FINDINGS

### Efficacy of the Internet-based cognitive behavioral therapy program

The positive results of our pilot test instigated the large scale RCT (Chapter 2). The results of this RCT indicate that iCBT, provided with or without therapist support, has a positive effect on the perceived impact of HF/NS, overall levels of menopausal symptoms, sleep quality, hot flush frequency, and night sweats frequency in BC survivors with treatment-induced menopausal symptoms (Chapter 4). Overall, estimates of the strength of the effects and the percentages of women with a clinically significant improvement in symptoms favored the guided over the self-managed iCBT group. Some of these treatment gains were lost at follow-up.

The compliance rates were, as hypothesized, higher than those reported in the previously conducted Dutch trial of Duijts and colleagues that evaluated the efficacy of group-based CBT in BC survivors with treatment-induced menopausal symptoms [1]. The strength of the effects observed in our trial was similar to that reported by Duijts et al. thus iCBT appears to be a viable alternative to group-based CBT in reducing menopausal symptom burden.

Our overall positive findings are in line with three previous UK-based RCTs that evaluated the efficacy of several formats of the CBT program on which our program was based in healthy women and BC survivors [2-4]. The strength of our effects and the percentages of women reporting a clinically significant reduction in symptoms in our trial were, however, lower than those observed in the UK-based studies. Contrary to the other studies,

participation in our study and the Duijts et al. trial [1] was limited to BC survivors experiencing treatment-induced menopausal symptoms, while the three other studies also included BC survivors and healthy women with naturally occurring menopausal symptoms [2-4]. Also, we observed a lower mean baseline score for the perceived impact of HF/NS in our trial than was the case in the earlier trials, thus resulting in less room for improvement. We believe that the differences in results most likely indicate that treatment-induced menopausal symptoms may be more resistant to change than naturally occurring symptoms [5, 6].

Our results also showed significant improvement over time in sleep quality for women allocated to the iCBT groups. However, at longer-term follow-up, about half of these women still scored above the threshold indicative of impaired sleep quality. This suggests the need to strengthen that component of the intervention targeting sleep quality.

Exploratory analyses indicated that the degree of compliance with either of the two iCBT formats was not associated significantly to changes over time in menopausal symptom burden. Although this seems somewhat counterintuitive and is not reflected in the findings of previous studies [7-9], it most likely stems from the fact that a high percentages of women, 80% and 90% in the self-managed and guided iCBT groups respectively, completing the three core modules of our iCBT program.

CBT is hypothesized to generate sustainable positive effects through the acquisition of new skills. The consolidation of positive effects of CBT on psychosocial and somatic outcomes has been supported by many individual studies and by meta-analyses [10-13]. The available evidence, however, is based primarily on traditional. face-to-face CBT, while less is known about the sustained effects of iCBT. In our study, we observed only a minor loss of treatment gains at longer-term follow-up. However, since our follow-up was relatively brief (6 months), we cannot assume that the observed positive effects will be maintained over a longer period of time. This is something that deserves further evaluation.



## Cost-effectiveness of the Internet-based cognitive behavioral therapy program

Economic evaluations can guide policymakers in deciding whether to (systematically) reimburse intervention costs and can assist institutions and healthcare professionals in deciding, if available, which specific intervention format to adopt [14]. Overall, the economic evaluation for

both iCBT formats indicated that: 1) the cost-utility ratios were well below the generally accepted €30.000 per quality-adjusted-life-year (QALY), 2) the costs to obtain a clinically relevant improvement in menopausal symptom burden were moderate, and 3) the estimated budget impact is trivial when compared to the medical treatment for cancer (Chapter 5). When comparing the results of the two formats of the iCBT program, all three types of economic evaluations tended to favor the self-managed format. The lower costs associated with the self-managed format appear to outweigh the slightly stronger effects on menopausal symptom burden observed for the guided format. The results of the economic evaluation of our guided iCBT program are comparable to those of the group-based CBT program investigated by Mewes and colleagues [15].

Dependent on the willingness to pay for improved care, these data support the implementation of the current iCBT program. This study, however, did not include (separate) analyses using direct and indirect healthcare costs solely associated with menopausal symptom burden. Two large scale cohort studies conducted in the United States, report annual direct per-patient costs of menopausal symptom burden of between $ 250 and $ 1,500, with the higher figure reflecting patients with untreated symptoms [16, 17]. These figures do not seem to differ between women experiencing natural versus treatment-induced menopausal symptoms [17]. In addition, reports on indirect costs attributable to work loss due to menopausal symptom burden are mixed, reporting no incremental costs or costs between $ 750 - $ 6.500 per person per year [17-19] Although all these studies are not without methodological limitations, taken together, the results clearly indicate a direct relationship between menopausal symptom burden and costs associated with healthcare utilization and work absenteeism. Additional analyses that only include costs associated directly with menopausal symptom burden may actually show a cost-saving effect of iCBT.

### Patient characteristics that moderate and therapeutic change mechanisms that mediate treatment effects

Since individuals can differ in their response to treatment, insight in characteristics that moderate these responses is highly valuable, especially when faced with scarce healthcare resources [20]. Results from our study indicated that, of a wide range of sociodemographic, clinical, menopause-related and psychosocial factors, only educational levels moderated

treatment effects (Chapter 6). Women with a high school or vocational degree benefited more from the iCBT program (both formats) in terms of a decrease in perceived impact of HF/NS than their counterparts in the control group, whereas this was not the case for women who completed college or university. This contrasts with findings from previous studies that either reported that highly educated women benefitted most or that a moderating effect of education was absent [5, 21-24]. A possible explanation for our finding is that highly educated women allocated to the control group may have sought alternative sources of information or strategies for dealing with their menopausal symptoms [25, 26]. Also, since the current program was designed to be comprehensible for all women irrespective of educational background, it may be that more highly educated women would have benefitted from a more sophisticated approach [26].

The iCBT program is hypothesized to result in, among other things, healthier beliefs and coping behaviors concerning HF/NS, and this proved to be the case. Three belief categories were assessed: beliefs about the feelings of embarrassment or feeling judged by others when experiencing hot flushes in a social context; beliefs about one's ability to influence the extent to which night sweats negatively impact sleep and daily functioning; and beliefs about one's ability to control and cope effectively with hot flushes. Women in the iCBT group developed healthier beliefs, compared to the control group, in all three categories and this, in turn, mediated our treatment effects. Hence, the development of healthier beliefs contributed to the positive results of the iCBT. Changes in coping behaviors and psychological distress, however, only showed a trend towards mediation of the treatment effects. These findings are in line with two previously conducted studies aimed at identifying moderators and mediators of group-based and minimally guided self-help CBT for healthy women and BC survivors with bothersome menopausal symptoms [5, 21]. This suggests that more effort should be devoted to strengthening the behavioral component of the CBT program.

## METHODOLOGICAL CONSIDERATIONS

The results of our research should be interpreted in light of its methodological strengths and limitations. The methodological strengths of this study include the randomized controlled design used to compare the efficacy of the iCBT program delivered, with and without therapist guidance, with usual care, the large sample size, the multicenter participation, the use of standardized outcome measures. and the limited loss to follow-up. The methodological limitations and considerations are related to the design of the study, the nature and quality of the assessments, and the iCBT program itself.

### Study design

Participating in an RCT can itself lead to favorable outcomes for women allocated to a waiting list control group. Information provided during the invitational and screening process, and the embedded suggestion that symptoms can be positively influenced, may encourage women in a control group to consult other sources of information to find ways to cope with their symptoms. In our study, we observed an improvement in the perceived impact of HF/NS in the control group, and especially in women with higher education levels. Although we assessed throughout the trial whether women in both the intervention and control groups undertook additional activities to reduce their menopausal symptom burden, we did not inquire about information-seeking behaviors. This potential contamination effect could have resulted in an underestimation of treatment effects.

Ideally, we would have included a third study arm in order to directly compare the effects of Internet-based and face-to-face group-based CBT in reducing menopausal symptom burden. However, this would only have been of value if we were to significantly improve the compliance rates for the group-based CBT format above those observed in the trial of Duijts and colleagues [1]. This was not something that we could guarantee. Also, the additional costs associated with an extra intervention group could not be absorbed by the available study budget. It would also have been desirable to directly compare the effects of the guided with the self-managed iCBT group. However, this would have required a much larger sample size in order to reach acceptable power to detect the hypothesized, small differences in treatment effects between these two formats [27].

## Assessments

Since the aim of the iCBT program was to help women cope with their menopausal symptoms, the efficacy of the program was primarily evaluated in terms of reduced symptom burden rather than symptom frequency. This limited our ability to compare the treatment effects in our trial with those of other trials in which the focus was on reducing the frequency of symptoms [28, 29].

Data regarding user engagement with Internet-based interventions are readily available through means of technical usage statistics (i.e. log data) [30, 31]. These log data can provide insight into many aspects of engagement, including the number of completed modules, time spent on the program and number of logins [30-33]. Technological caveats hindered the exploration of certain types of log data in our trial. For example, we discovered that the frequency of logins per and across modules metric was confounded with diary entries, but only for some women. Fortunately, we did not rely solely on log data, but also assessed aspects of patient engagement via the post-iCBT follow-up self-report questionnaire. We observed a high correlation between the available log data and self-report data concerning the number of modules completed ($r > .9$). This suggests that the additional self-report data about program engagement was quite accurate. Rapidly emerging technological advances increasingly allow for more sophisticated log data to be obtained [34]. Such detailed log data, can, for example, inform us about the level of engagement with specific in-module sections.

Health-related quality of life (HRQOL) is an important outcome in many behavioral trials and can be assessed with a range of questionnaires. Overall, these questionnaires either cover generic HRQOL or condition-specific HRQOL [35]. In the current study, we chose the former type (generic HRQOL) because the available condition-specific questionnaires such as the European Organisation for Research and Treatment of Cancer core questionnaire (EORTC QLQ-C30) primarily assess acute treatment-related side-effects and thus may be less appropriate for longer-term survivors such as those included in our trial [35-37]. Nonetheless, a generic HRQOL may also be of limited use since it might not be able to capture relevant cancer survivorship issues and related improvements over time. Currently, the EORTC Quality of Life Group is developing an HRQOL assessment approach more suitable for these longer-term cancer survivors [36].

In order to obtain utility scores for the cost-utility analyses, we had to transform our HRQOL data into a single preference-based EQ-5D score [38]. Two large scale studies provided algorithms for this transformation, resulting in reliable and fairly accurate EQ-5D scores [39, 40]. This was, however, based on data from populations with different health conditions than experienced by our participants. To avoid potential bias, direct administration of the EQ-5D remains the preferred method [39, 41].

The EQ-5D utility score is also used to calculate a generic summary measure of health outcomes, i.e. QALYs, used in cost-utility analyses. The universal use of such a measure increases the comparability of economic evaluations across health care problems and is mandatory for financial reimbursement by, for example, the National Institute for Health and Clinical Excellence and the Health Institute in the Netherlands [42]. However, the use of generic preference-based measures of health to calculate QALYs has been criticized since they are likely to be unresponsive to condition-specific changes, and thus may not capture meaningful improvements [42-44]. This dissonance can also be observed in the current study. That is, our results indicated only minor improvement in health utility scores over time, while the perceived impact of HF/NS and overall levels of menopausal symptoms changed significantly. We believe that cost-utility analyses may be less useful than cost-effectiveness analyses when evaluating behavioral interventions such as those investigated in our trial. Cost-effectiveness studies focus primarily on and are driven by more proximal, clinically relevant outcomes. We would note that there are ongoing efforts to develop condition-specific preference-based instruments and to map algorithms to supplement the traditional QALY approach [42]. This will hopefully increase the relevance of cost-utility analyses in similar psychosocial and behavioral intervention studies.

Our study also had some limitations in terms of the (lack of) available healthcare and societal data. Both were assessed at short- and longer-term follow-up, but not at baseline. Although this was sufficient to conduct the economic evaluation, the lack of baseline data hampered additional exploratory analyses. We could not, for example, explore whether there was a relative decline in healthcare consumption throughout study participation, especially for women allocated to the intervention groups. We also did not have data on the reasons for healthcare utilization and productivity losses. That is, we assessed visits to a range of healthcare professionals but did not inquire whether these visits were related to the

respondents' menopausal symptoms. Therefore the healthcare costs used in the economic evaluation may not have necessarily reflected the costs associated with the menopausal symptom burden and, thus, the costs associated with the different formats of the iCBT program. Since the reasons for production losses were also unknown, and the data seemed to be mainly driven by comorbid health conditions, we had to exclude the corresponding societal perspective from our analyses. We also lacked data on the frequency of medication intake, and thus excluded this type of healthcare consumption from the economic evaluation. However, based on the economic evaluation of the group-based CBT program, medication uptake is expected to be relatively low, thus having a small additional effect on the overall healthcare costs [15].

The current study and the previous studies of group-based CBT had follow-up periods of 6 months [1, 2, 4]. Longer-term assessments, e.g. one or two years after baseline, could provide valuable insights and could confirm whether iCBT leads to sustained positive effects. This is particularly relevant given the chronicity of menopausal symptoms after BC treatment, especially for younger women undergoing maintenance endocrine treatment [45].

### Form and content of the Internet-based cognitive behavioral therapy program

The iCBT program we evaluated is well-grounded in relevant psychological theories and incorporates elements of symptom perception theory, self-regulation theory and cognitive behavioral theories [46]. It includes multiple evidence-based behavioral change techniques, such as modeling helpful behavior by means of videos and stories of peers. Exploratory analyses of user-engagement with our iCBT program suggest that engagement with elements that required continued effort, like the practice of relaxation and goal attainment, could be improved, especially in the self-managed group.

Adding behavioral change techniques could increase user-engagement and efficacy of the current program [47-49]. A recent and promising approach concerns the use of traditional behavior change techniques, but providing them via modern gaming elements [50, 51]. For example, a rewarding system could be introduced, and users can 'level-up' by performing behaviors like relaxation, which in turn could unlock additional program content. By creating a virtual guide or adding biofeedback user-engagement could further be increased. Although still in its infancy, several studies have demonstrated the benefits of Internet-based interventions

that integrated gaming elements in increasing health-promoting behaviors and in improving mental health [52-55].

In our trial, prompts to increase continued engagement were stated in very general terms, i.e. 'A new week of the Eva-Online program starts today. We wish you good luck with this week's module'. We believe that engagement with the different program elements could be improved by tailoring the content of these reminders to the patients' progress (by use of algorithms) and/or by stressing the importance of the daily practice of challenging unhelpful beliefs and applying several behavior change techniques [56-58]. Tailoring the frequency of the reminders, but also the content of the modules to correspond to individuals' needs, could further improve engagement [59-61].

Lastly, all the above suggested changes would benefit from making the program available as a smartphone application.

## FUTURE DEVELOPMENTS IN RESEARCH AND PRACTICE

The ultimate goal of establishing the efficacy of certain interventions in large scale RCTs is to improve patient care. Translating positively evaluated interventions into clinical health care has, however, proven to be challenging [62-64]. In this last section we will reflect on research and clinical implications from a broader perspective, all directed towards facilitating the actual uptake of our and other interventions.

### Translation of evidence-based interventions into different formats and settings

Ample studies have shown that Internet-based interventions can be effective for a range of psychosocial and somatic problems [7, 65-68]. These Internet-based interventions are often based on evidence-based, face-to-face formats. Studies have demonstrated that they have the potential to be as effective as these in-person formats [69-71]. This raises the question whether changing formats, i.e. from face-to-face to Internet-based, requires extensive program evaluation as is the case with large scale RCTs.

Although some aspects of a face-to-face intervention, including the theoretical framework, the overall content and the aim of homework assignments, will typically remain unchanged when translating a face-

to-face intervention to an Internet-based format, other characteristics may be altered, added or even removed. The most discussed aspect of this translation process is the need for therapist support. Internet-based interventions with therapist support are often reported to result in superior effects than a self-managed format [7-9]. However, studies directly comparing two identical programs that only vary in terms of the presence or amount of therapist support show, in line with our findings, largely similar outcomes [72-75]. Thus, therapist support is not a necessarily precondition for successful translation. A number of studies have demonstrated that Internet-based interventions result in stronger effects if they are accessible via a closed system, interactive, user-friendly, tailored to the individual, and include reminders [57, 60, 65, 76-78]. Further investigation is needed to identify additional characteristics of Internet-based interventions that are critical to its efficacy. In addition, we would propose a user-centered design incorporating rapid and iterative prototype development and testing, in close collaboration with the expected users, in order to address and optimize the human-technology interaction and optimize the impact of Internet-based interventions [50].

We would advocate careful consideration of the need for carrying out large scale RCTs when translating face-to-face interventions to an Internet-based format. While the time, effort and expense involved in such a rigorous evaluation may be necessary, there may be situations where other research designs may be sufficient. For example, programs with a] a well-established evidence-base, albeit in a face-to-face format, that b] have been developed and tested using an user-centered design could qualify for a more pragmatic research approach. For example, a one-group, pre-post test design might be sufficient to provide additional evidence regarding efficacy and user experience. Such an approach could possibly be used to evaluate our iCBT program when delivered to a more heterogeneous group of cancer survivors, i.e. older BC survivors and gynecological cancer survivors whose lives are also affected by menopausal symptoms.



## Towards a transdiagnostic treatment approach

Comorbidity of physical and mental health problems is not uncommon across patient populations. Younger BC survivors with menopausal symptoms are no exception and are at risk for developing comorbid problems like psychological distress, sexual problems and fatigue [35, 36, 79-83]. However, most interventions are designed to tackle only one

specific problem. It might be both more effective and more efficient to tackle several, related or clustered clinical problems in a single intervention program.

Based on the overlap of techniques used to treat a variety of problems, Barlow and colleagues suggest that such a unified approach should focus on emotion-regulation by including three overarching core elements, i.e. 1] 'altering antecedent cognitive appraisal', 2] 'modifying emotion-driven behaviors' and 3] 'preventing emotional avoidance' [84-86]. This, in turn, closely resembles the core principles of CBT. As such, interventions that were initially developed to be problem-specific, but contain these elements, could, if needed, be integrated. Several studies have demonstrated positive effects of these transdiagnostic iCBT programs for the treatment of anxiety and mood disorders [60, 61, 74, 87, 88].

We are aware of two evidence-based Internet-based interventions, both self-managed, available in the Netherlands that address a multitude of physical and mental health problems in cancer survivors. These are the 'Breath' (Op Adem Na Borstkanker) and 'Cancer Aftercare Guide' (Kanker Nazorg Wijzer) programs [89-91]. Integrating our iCBT intervention (self-managed format) with either of these two programs is feasible given the common use of the core elements (as described above) and has the potential to further increase the HRQOL of cancer survivors. Such integration could result in a better use of (financial) resources.

The development of such a transdiagnostic Internet-based intervention is not without challenges. This concerns, for example, the selection of relevant modules and the interdependence of these modules. Using well-evaluated, high quality algorithms would therefore be necessary for optimal use of these interventions [92, 93].

## Bridging the research - practice gap

It is widely acknowledged that many evidence-based interventions are not integrated into clinical care [62-64]. This also concerns psychosocial care for cancer patients and survivors [94-96]. Ample theories, models and frameworks have been developed to facilitate the successful implementation of evidence-based interventions, with process models providing the most practical guidance in selecting and applying implementation facilitating strategies [97-99]. The knowledge to action (KTA) framework represents a very thorough example of such a process model that specifically addresses the gap between research and practice [100]. This framework is based on

over 60 action models and consists of two distinct but related processes, i.e. knowledge creation and action, each comprising several fluid and iterative phases. An essential prerequisite of this framework is the collaboration among different stakeholders. As such, identifying all relevant stakeholders should comprise the first step towards successful implementation. Among the action steps, this collaboration is also of particular relevance for assessing barriers and facilitating factors of program uptake. That is, stakeholders provide unique experiences and insights into the barriers impeding successful implementation. These barriers, as put forward by Grol and Wensing [101], should be assessed at the level of the innovation, the individual professional, the patient, and the social, organizational, economic and political context. For example, awareness of the intervention, the organization of care processes and financial factors can impact on the uptake of an intervention. In response, tailored strategies can be instigated to overcome the identified barriers [101]. Taken together, these and other action models/frameworks provide practical guidance in selecting and applying implementation facilitating steps and strategies.

Most of the implementation models, however, present a number of steps that often originate after demonstrating the evidence-base for an intervention. We would advocate this process to start at the beginning of a research cycle, and especially at the developmental phase of an intervention as proposed in the Dutch 'Opschalingsgids psychosociale oncologie' [102]. This not only poses clear benefits in terms of timespan, it also creates the opportunity to make choices that can ultimately facilitate instead of hamper the uptake of interventions in clinical care. For example, developing an online intervention on a commonly used, reliable healthcare platform, instead of a platform solely used for research purposes, will positively impact implementation. In addition, in response to the current lack of financial reimbursement of Internet-based self-managed interventions in the Netherlands, activities can be (collectively) undertaken, for example lobbying activities, early on, making it more likely that this barrier will be overcome by the time the randomized controlled trial is completed [102].

As a concluding remark, we strongly believe that collaboration between stakeholders, including scientists, health care professionals and experts in the field of healthcare regulations, is critical at the beginning of and throughout the research cycle to facilitate the implementation process and thus, ultimately, to provide state of the art psychosocial care and support for cancer patients and survivors.

## REFERENCES


[1] S.F.A. Duijts, M. Van Beurden, H.S.A. Oldenburg, M.S. Hunter, J.M. Kieffer, M.M. Stuiver, M.A. Gerritsma, M.B.E. Menke-Pluymers, P.W. Plaisir, H. Rijna, A.M.F. Lopes Cardozo, G.J. Timmers, S. Van der Meij, H. Van der Veen, N. Bijker, L.M. De Widt-Levert, M.M. Geenen, G. Heuff, E.J. Van Dulken, E. Boven, N.K. Aaronson, Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: Results of a randomized controlled multicenter trial., Journal of Clinical Oncology 30(33) (2012) 4124-4133.

[2] B. Ayers, M. Smith, J. Hellier, E. Mann, M.S. Hunter, Effectiveness of group and self-help cognitive behavior therapy in reducing problematic menopausal hot flushes and night sweats (MENOS 2): a randomized controlled trial, Menopause 19(7) (2012) 749-759.

[3] C. Hardy, A. Griffiths, S. Norton, M.S. Hunter, Self-help cognitive behavior therapy for working women with problematic hot flushes and night sweats (MENOS@ Work): a multicenter randomized controlled trial, Menopause 25(5) (2018) 508-519.

[4] E. Mann, M.J. Smith, J. Hellier, J.A. Balabanovic, H. Hamed, E.A. Grunfeld, M.S. Hunter, Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial, Lancet Oncol 13(3) (2012) 309-318.

[5] J. Chilcot, S. Norton, M.S. Hunter, Cognitive behaviour therapy for menopausal symptoms following breast cancer treatment: Who benefits and how does it work?, Maturitas 78(1) (2014) 56-61.

[6] V. Morton, D.J. Torgerson, Effect of regression to the mean on decision making in health care, BMJ (Clinical research ed.) 326(7398) (2003) 1083-4.

[7] V. Spek, P. Cuijpers, I. Nyklicek, H. Riper, J. Keyzer, V. Pop, Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis, Psychol Med 37(3) (2007) 319-28.

[8] B. Palmqvist, P. Carlbring, G. Andersson, Internet-delivered treatments with or without therapist input: does the therapist factor have implications for efficacy and cost?, Expert review of pharmacoeconomics & outcomes research 7(3) (2007) 291-7.

[9] H. Baumeister, L. Reichler, M. Munzinger, J. Lin, The impact of guidance on Internet-based mental health interventions — A systematic review, Internet Interventions 1(4) (2014) 205-215.

[10] P. Cuijpers, S.D. Hollon, A. van Straten, C. Bockting, M. Berking, G. Andersson, Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis, BMJ open 3(4) (2013).

[11] S.D. Hollon, M.O. Stewart, D. Strunk, Enduring effects for cognitive behavior therapy in the treatment of depression and anxiety, Annual review of psychology 57 (2006) 285-315.

[12] H. Faller, M. Schuler, M. Richard, U. Heckl, J. Weis, R. Kuffner, Effects of psycho-oncologic interventions on emotional distress and quality of life in adult patients with cancer: systematic review and meta-analysis, J Clin Oncol 31(6) (2013) 782-93.
[13] P.J. Batterham, H. Christensen, A.J. Mackinnon, J.A. Gosling, F.P. Thorndike, L.M. Ritterband, N. Glozier, K.M. Griffiths, Trajectories of change and long-term outcomes in a randomised controlled trial of internet-based insomnia treatment to prevent depression, BJPsych open 3(5) (2017) 228-235.
[14] A. Brennan, R. Akehurst, Modelling in health economic evaluation. What is its place? What is its value?, PharmacoEconomics 17(5) (2000) 445-59.
[15] J.C. Mewes, W.H. van Harten, S.F. Duijts, H.S. Oldenburg, M. Van Beurden, M.M. Stuiver, M.S. Hunter, J.M. Kieffer, L.M.G. Steuten, N.K. Aaronson, Cost-effectiveness of cognitive behavioral therapy and physical exercise for alleviating treatment-induced menopausal symptoms in breast cancer patients, 2013.
[16] A.R. Assaf, A.G. Bushmakin, N. Joyce, M.J. Louie, M. Flores, M. Moffatt, The Relative Burden of Menopausal and Postmenopausal Symptoms versus Other Major Conditions: A Retrospective Analysis of the Medical Expenditure Panel Survey Data, American health & drug benefits 10(6) (2017) 311-321.
[17] P. Sarrel, D. Portman, P. Lefebvre, M.H. Lafeuille, A.M. Grittner, J. Fortier, J. Gravel, M.S. Duh, P.M. Aupperle, Incremental direct and indirect costs of untreated vasomotor symptoms, Menopause 22(3) (2015) 260-6.
[18] N.L. Kleinman, N.J. Rohrbacker, A.G. Bushmakin, J. Whiteley, W.D. Lynch, S.N. Shah, Direct and indirect costs of women diagnosed with menopause symptoms, Journal of occupational and environmental medicine 55(4) (2013) 465-70.
[19] J. Whiteley, J.S. Wagner, A. Bushmakin, L. Kopenhafer, M. Dibonaventura, J. Racketa, Impact of the severity of vasomotor symptoms on health status, resource use, and productivity, Menopause 20(5) (2013) 518-24.
[20] H.C. Kraemer, G.T. Wilson, C.G. Fairburn, W.S. Agras, Mediators and moderators of treatment effects in randomized clinical trials, Archives of general psychiatry 59(10) (2002) 877-83.
[21] S. Norton, J. Chilcot, M.S. Hunter, Cognitive-behavior therapy for menopausal symptoms (hot flushes and night sweats): moderators and mediators of treatment effects, Menopause-J. N. Am. Menopause Soc. 21(6) (2014) 574-578.
[22] J. Kalter, I.M. Verdonck-de Leeuw, M.G. Sweegers, N.K. Aaronson, P.B. Jacobsen, R.U. Newton, K.S. Courneya, J.F. Aitken, J. Armes, C. Arving, L.J. Boersma, A.M.J. Braamse, Y. Brandberg, S.K. Chambers, J. Dekker, K. Ell, R.J. Ferguson, M.F.M. Gielissen, B. Glimelius, M.M. Goedendorp, K.D. Graves, S.P. Heiney, R. Horne, M.S. Hunter, B. Johansson, M.L. Kimman, H. Knoop, K. Meneses, L.L. Northouse, H.S. Oldenburg, J.B. Prins, J. Savard, M. van Beurden, S.W. van den Berg, J. Brug, L.M. Buffart, Effects and moderators of psychosocial interventions on quality of life, and emotional and social function in patients with cancer: An individual patient data meta-analysis of 22 RCTs, Psychooncology 27(4) (2018) 1150-1161.

[23] J.E. Broderick, F.J. Keefe, S. Schneider, D.U. Junghaenel, P. Bruckenthal, J.E. Schwartz, A.T. Kaell, D.S. Caldwell, D. McKee, E. Gould, Cognitive behavioral therapy for chronic pain is effective, but for whom?, Pain 157(9) (2016) 2115-23.
[24] N. Vincent, K. Walsh, S. Lewycky, Determinants of success for computerized cognitive behavior therapy: examination of an insomnia program, Behavioral sleep medicine 11(5) (2013) 328-42.
[25] J. Fogel, S.M. Albert, F. Schnabel, B.A. Ditkoff, A.I. Neugut, Use of the Internet by women with breast cancer, Journal of medical Internet research 4(2) (2002) E9.
[26] D.R. Longo, Understanding health information, communication, and information seeking of patients and consumers: a comprehensive and integrated model, Health expectations : an international journal of public participation in health care and health policy 8(3) (2005) 189-94.
[27] J. Cohen, Statistical power analysis for the behavioral sciences, Lawrence Earlbaum Associates, Hillsdale, New Jersey, 1988.
[28] C.L. Loprinzi, J. Sloan, V. Stearns, R. Slack, M. Iyengar, B. Diekmann, G. Kimmick, J. Lovato, P. Gordon, K. Pandya, T. Guttuso, Jr., D. Barton, P. Novotny, Newer antidepressants and gabapentin for hot flashes: an individual patient pooled analysis, J Clin Oncol 27(17) (2009) 2831-2837.
[29] D.W. Sturdee, M.S. Hunter, P.M. Maki, P. Gupta, J. Sassarini, J.C. Stevenson, M.A. Lumsden, The menopausal hot flush: a review, Climacteric (2017) 1-10.
[30] J.E. Van Gemert-Pijnen, S.M. Kelders, E.T. Bohlmeijer, Understanding the Usage of Content in a Mental Health Intervention for Depression: An Analysis of Log Data, 16(1) (2014) e27.
[31] S.W. van den Berg, E.J. Peters, J.F. Kraaijeveld, M.F.M. Gielissen, J.B. Prins, Usage of a Generic Web-Based Self-Management Intervention for Breast Cancer Survivors: Substudy Analysis of the BREATH Trial, Journal of medical Internet research 15(8) (2013) 11.
[32] L. Donkin, H. Christensen, S.L. Naismith, B. Neal, I.B. Hickie, N. Glozier, A systematic review of the impact of adherence on the effectiveness of e-therapies, Journal of medical Internet research 13(3) (2011) e52.
[33] G. Eysenbach, CONSORT-EHEALTH: improving and standardizing evaluation reports of Web-based and mobile health interventions, Journal of medical Internet research 13(4) (2011) e126.
[34] L. Yardley, B.J. Spring, H. Riper, L.G. Morrison, D.H. Crane, K. Curtis, G.C. Merchant, F. Naughton, A. Blandford, Understanding and Promoting Effective Engagement With Digital Behavior Change Interventions, American journal of preventive medicine 51(5) (2016) 833-842.
[35] N.K. Aaronson, V. Mattioli, O. Minton, J. Weis, C. Johansen, S.O. Dalton, I.M. Verdonck-de Leeuw, K.D. Stein, C.M. Alfano, A. Mehnert, A. de Boer, L.V. van de Poll-Franse, Beyond treatment - Psychosocial and behavioural issues in cancer survivorship research and practice, EJC supplements : EJC : official journal of EORTC, European Organization for Research and Treatment of Cancer ... [et al.] 12(1) (2014) 54-64.

[36] M. van Leeuwen, O. Husson, P. Alberti, J.I. Arraras, O.L. Chinot, A. Costantini, A.S. Darlington, L. Dirven, M. Eichler, E.B. Hammerlid, B. Holzner, C.D. Johnson, M. Kontogianni, T.K. Kjaer, O. Morag, S. Nolte, A. Nordin, A. Pace, M. Pinto, K. Polz, J. Ramage, J.C. Reijneveld, S. Serpentini, K.A. Tomaszewski, V. Vassiliou, I.M. Verdonck-de Leeuw, I. Vistad, T.E. Young, N.K. Aaronson, L.V. van de Poll-Franse, Understanding the quality of life (QOL) issues in survivors of cancer: towards the development of an EORTC QOL cancer survivorship questionnaire, Health and quality of life outcomes 16(1) (2018) 114.

[37] N.K. Aaronson, S. Ahmedzai, B. Bergman, M. Bullinger, A. Cull, N.J. Duez, A. Filiberti, H. Flechtner, S.B. Fleishman, J.C. de Haes, et al., The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology, J Natl Cancer Inst 85(5) (1993) 365-76.

[38] P. Dolan, Modeling valuations for EuroQol health states, Med Care 35(11) (1997) 1095-108.

[39] R. Ara, J. Brazier, Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available), Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 11(7) (2008) 1131-43.

[40] D. Rowen, J. Brazier, J. Roberts, Mapping SF-36 onto the EQ-5D index: how reliable is the relationship?, Health and quality of life outcomes 7 (2009) 27.

[41] R. Ara, D. Rowen, C. Mukuria, The Use of Mapping to Estimate Health State Utility Values, PharmacoEconomics 35(Suppl 1) (2017) 57-66.

[42] B.F.M. Wijnen, I. Mosweu, M. Majoie, L. Ridsdale, R.J.A. de Kinderen, S. Evers, P. McCrone, A comparison of the responsiveness of EQ-5D-5L and the QOLIE-31P and mapping of QOLIE-31P to EQ-5D-5L in epilepsy, The European journal of health economics : HEPAC : health economics in prevention and care 19(6) (2018) 861-870.

[43] S.J. Whitehead, S. Ali, Health outcomes in economic evaluation: the QALY and utilities, British medical bulletin 96 (2010) 5-21.

[44] L. Lenert, R.M. Kaplan, Validity and interpretation of preference-based measures of health-related quality of life, Med Care 38(9 Suppl) (2000) Ii138-50.

[45] S.R. Davis, M. Panjari, P.J. Robinson, P. Fradkin, R.J. Bell, Menopausal symptoms in breast cancer survivors nearly 6 years after diagnosis, Menopause 21(10) (2014) 1075-81.

[46] M.S. Hunter, E. Mann, A cognitive model of menopausal hot flushes and night sweats, J Psychosom Res 69(5) (2010) 491-501.

[47] T.L. Webb, J. Joseph, L. Yardley, S. Michie, Using the internet to promote health behavior change: a systematic review and meta-analysis of the impact of theoretical basis, use of behavior change techniques, and mode of delivery on efficacy, Journal of medical Internet research 12(1) (2010) e4.

[48] G. Kok, N.H. Gottlieb, G.J. Peters, P.D. Mullen, G.S. Parcel, R.A. Ruiter, M.E. Fernandez, C. Markham, L.K. Bartholomew, A taxonomy of behaviour change methods: an Intervention Mapping approach, Health psychology review 10(3) (2016) 297-312.
[49] S. Michie, M. Richardson, M. Johnston, C. Abraham, J. Francis, W. Hardeman, M.P. Eccles, J. Cane, C.E. Wood, The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions, Ann Behav Med 46(1) (2013) 81-95.
[50] T.M. Fleming, D. de Beurs, Y. Khazaal, A. Gaggioli, G. Riva, C. Botella, R.M. Banos, F. Aschieri, L.M. Bavin, A. Kleiboer, S. Merry, H.M. Lau, H. Riper, Maximizing the Impact of e-Therapy and Serious Gaming: Time for a Paradigm Shift, Frontiers in psychiatry 7 (2016) 65.
[51] C. Cheek, T. Fleming, M.F. Lucassen, H. Bridgman, K. Stasiak, M. Shepherd, P. Orpin, Integrating Health Behavior Theory and Design Elements in Serious Games, JMIR mental health 2(2) (2015) e11.
[52] A. Shah, K.R. Kraemer, C.R. Won, S. Black, W. Hasenbein, Developing Digital Intervention Games for Mental Disorders: A Review, Games for health journal 7(4) (2018) 213-224.
[53] T.M. Fleming, C. Cheek, S.N. Merry, H. Thabrew, H. Bridgman, K. Stasiak, M. Shepherd, Y. Perry, S. Hetrick, Serious games for the treatment or prevention of depression: A systematic review, Revista de Psicopatologia y Psicologia Clinica 19(3) (2014) 227-242.
[54] H.M. Lau, J.H. Smit, T.M. Fleming, H. Riper, Serious Games for Mental Health: Are They Accessible, Feasible, and Effective? A Systematic Review and Meta-analysis, Frontiers in psychiatry 7 (2016) 209.
[55] L. Sardi, A. Idri, J.L. Fernandez-Aleman, A systematic review of gamification in e-Health, Journal of biomedical informatics 71 (2017) 31-48.
[56] L.M. Ritterband, F.P. Thorndike, D.J. Cox, B.P. Kovatchev, L.A. Gonder-Frederick, A behavior change model for internet interventions, Ann Behav Med 38(1) (2009) 18-27.
[57] G. Alkhaldi, F.L. Hamilton, R. Lau, R. Webster, S. Michie, E. Murray, The Effectiveness of Prompts to Promote Engagement With Digital Interventions: A Systematic Review, Journal of medical Internet research 18(1) (2016) 14.
[58] L. Donkin, N. Glozier, Motivators and motivations to persist with online psychological interventions: a qualitative study of treatment completers, Journal of medical Internet research 14(3) (2012) e91.
[59] A.C. Zarski, D. Lehr, M. Berking, H. Riper, P. Cuijpers, D.D. Ebert, Adherence to Internet-Based Mobile-Supported Stress Management: A Pooled Analysis of Individual Participant Data From Three Randomized Controlled Trials, Journal of medical Internet research 18(6) (2016) e146.
[60] C.A. Webb, I.M. Rosso, S.L. Rauch, Internet-Based Cognitive-Behavioral Therapy for Depression: Current Progress and Future Directions, Harvard review of psychiatry 25(3) (2017) 114-122.

[61] G. Andersson, N. Titov, Advantages and limitations of Internet-based interventions for common mental disorders, World psychiatry : official journal of the World Psychiatric Association (WPA) 13(1) (2014) 4-11.
[62] J.M. Grimshaw, M.P. Eccles, J.N. Lavis, S.J. Hill, J.E. Squires, Knowledge translation of research findings, Implementation science : IS 7 (2012) 50.
[63] R. Grol, Successes and failures in the implementation of evidence-based guidelines for clinical practice, Med Care 39(8 Suppl 2) (2001) Ii46-54.
[64] L.J. Cochrane, C.A. Olson, S. Murray, M. Dupuis, T. Tooman, S. Hayes, Gaps between knowing and doing: understanding and assessing the barriers to optimal health care, The Journal of continuing education in the health professions 27(2) (2007) 94-102.
[65] A. Barak, L. Hen, M. Boniel-Nissim, N.a. Shapira, A Comprehensive Review and a Meta-Analysis of the Effectiveness of Internet-Based Psychotherapeutic Interventions, Journal of Technology in Human Services 26(2-4) (2008) 109-160.
[66] P. Cuijpers, A. van Straten, G. Andersson, Internet-administered cognitive behavior therapy for health problems: A systematic review., J. Behav. Med. Vol.31(2) (2008) 169-177.
[67] G. Andersson, Using the Internet to provide cognitive behaviour therapy, Behav. Res. Ther. 47(3) (2009) 175-180.
[68] K.E. Post, J. Flanagan, Web based survivorship interventions for women with breast cancer: An integrative review, European Journal of Oncology Nursing 25 (2016) 90-99.
[69] P. Carlbring, G. Andersson, P. Cuijpers, H. Riper, E. Hedman-Lagerlof, Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: an updated systematic review and meta-analysis, Cogn Behav Ther 47(1) (2018) 1-18.
[70] G. Andersson, P. Cuijpers, P. Carlbring, H. Riper, E. Hedman, Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis, World psychiatry : official journal of the World Psychiatric Association (WPA) 13(3) (2014) 288-95.
[71] G. Andrews, P. Cuijpers, M.G. Craske, P. McEvoy, N. Titov, Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: a meta-analysis, PLoS One 5(10) (2010) e13196.
[72] T. Berger, F. Caspar, R. Richardson, B. Kneubühler, D. Sutter, G. Andersson, Internet-based treatment of social phobia: A randomized controlled trial comparing unguided with two types of guided self-help, Behav. Res. Ther. 49(3) (2011) 158-169.
[73] T. Berger, K. Hammerli, N. Gubser, G. Andersson, F. Caspar, Internet-based treatment of depression: a randomized controlled trial comparing guided with unguided self-help, Cogn Behav Ther 40(4) (2011) 251-66.

[74] B.F. Dear, L.G. Staples, M.D. Terides, V.J. Fogliati, J. Sheehan, L. Johnston, R. Kayrouz, R. Dear, P.M. McEvoy, N. Titov, Transdiagnostic versus disorder-specific and clinician-guided versus self-guided internet-delivered treatment for Social Anxiety Disorder and comorbid disorders: A randomized controlled trial, J Anxiety Disord 42 (2016) 30-44.
[75] V.J. Fogliati, B.F. Dear, L.G. Staples, M.D. Terides, J. Sheehan, L. Johnston, R. Kayrouz, R. Dear, P.M. McEvoy, N. Titov, Disorder-specific versus transdiagnostic and clinician-guided versus self-guided internet-delivered treatment for panic disorder and comorbid disorders: A randomized controlled trial, J Anxiety Disord 39 (2016) 88-102.
[76] G. Alkhaldi, K. Modrow, F. Hamilton, K. Pal, J. Ross, E. Murray, Promoting Engagement With a Digital Health Intervention (HeLP-Diabetes) Using Email and Text Message Prompts: Mixed-Methods Study, Interactive journal of medical research 6(2) (2017) e14.
[77] N. Titov, B.F. Dear, L. Johnston, C. Lorian, J. Zou, B. Wootton, J. Spence, P.M. McEvoy, R.M. Rapee, Improving adherence and clinical outcomes in self-guided internet treatment for anxiety and depression: randomised controlled trial, PLoS One 8(7) (2013) e62873.
[78] G. Andersson, P. Carlbring, T. Berger, J. Almlov, P. Cuijpers, What makes Internet therapy work?, Cogn Behav Ther 38 Suppl 1 (2009) 55-60.
[79] C.L. Shapiro, A. Recht, Side effects of adjuvant treatment of breast cancer., N Engl J Med 344(26) (2001) 1997-2008.
[80] I.K.N. (IKNL), Kankerzorg in beeld: over leven met en na kanker. <https://www.iknl.nl/docs/default-source/shop-downloads/kib-2019.pdf?sfvrsn=3>, 2019 2019).
[81] P.A. Ganz, J.H. Rowland, K. Desmond, B.E. Meyerowitz, G.E. Wyatt, Life after breast cancer: Understanding women's health-related quality of life and sexual functioning, Journal of Clinical Oncology 16(2) (1998) 501-514.
[82] L.B. Wenzel, D.L. Fairclough, M.J. Brady, D. Cella, K.M. Garrett, B.C. Kluhsman, L.A. Crane, A.C. Marcus, Age-related differences in the quality of life of breast carcinoma patients after treatment, Cancer 86(9) (1999) 1768-74.
[83] N.E. Avis, B. Levine, M.J. Naughton, D.L. Case, E. Naftalis, K.J. Van Zee, Explaining age-related differences in depression following breast cancer diagnosis and treatment, Breast Cancer Res Treat 136(2) (2012) 581-91.
[84] E.B. Moses, D.H. Barlow, A new unified treatment approach for emotional disorders based on emotion science, Curr. Dir. Psychol. 15(3) (2006) 146-150.
[85] D.H. Barlow, L.B. Allen, M.L. Choate, Toward a unified treatment for emotional disorders, Behavior therapy 35(2) (2004) 205-230.
[86] P.J. Norton, D.J. Paulus, Toward a Unified Treatment for Emotional Disorders: Update on the Science and Practice, Behavior therapy 47(6) (2016) 854-868.
[87] G. Andersson, The promise and pitfalls of the internet for cognitive behavioral therapy, BMC medicine 8 (2010) 82.
[88] N. Titov, G. Andrews, L. Johnston, E. Robinson, J. Spence, Transdiagnostic Internet treatment for anxiety disorders: A randomized controlled trial, Behav Res Ther 48(9) (2010) 890-9.

[89] S.W. van den Berg, M.F. Gielissen, J.A. Custers, W.T. van der Graaf, P.B. Ottevanger, J.B. Prins, BREATH: Web-Based Self-Management for Psychological Adjustment After Primary Breast Cancer--Results of a Multicenter Randomized Controlled Trial, J Clin Oncol 33(25) (2015) 2763-71.
[90] R.A. Willems, I. Mesters, L. Lechner, I.M. Kanera, C.A.W. Bolman, Long-term effectiveness and moderators of a web-based tailored intervention for cancer survivors on social and emotional functioning, depression, and fatigue: randomized controlled trial, Journal of cancer survivorship : research and practice 11(6) (2017) 691-703.
[91] R.A. Willems, C.A. Bolman, I. Mesters, I.M. Kanera, A.A. Beaulen, L. Lechner, Short-term effectiveness of a web-based tailored intervention for cancer survivors on quality of life, anxiety, depression, and fatigue: randomized controlled trial, Psychooncology 26(2) (2017) 222-230.
[92] I.M. Kanera, R.A. Willems, C.A. Bolman, I. Mesters, V. Zambon, B.C. Gijsen, L. Lechner, Use and Appreciation of a Tailored Self-Management eHealth Intervention for Early Cancer Survivors: Process Evaluation of a Randomized Controlled Trial, Journal of medical Internet research 18(8) (2016) e229.
[93] B.F. Chorpita, E.L. Daleiden, J.R. Weisz, Modularity in the design and application of therapeutic interventions, Applied & Preventive Psychology 11(3) (2005) 141-156.
[94] Y. Leykin, S.M. Thekdi, D.M. Shumay, R.F. Munoz, M. Riba, L.B. Dunn, Internet interventions for improving psychological well-being in psycho-oncology: review and recommendations, Psychooncology 21(9) (2012) 1016-25.
[95] K.C. Williams, B.M. Brothers, M.M. Ryba, B.L. Andersen, Implementing evidence-based psychological treatments for cancer patients, Psychooncology 24(12) (2015) 1618-25.
[96] S. Redman, J. Turner, C. Davis, Improving supportive care for women with breast cancer in Australia: the challenge of modifying health systems, Psychooncology 12(6) (2003) 521-31.
[97] P. Nilsen, Making sense of implementation theories, models and frameworks, Implementation science : IS 10 (2015) 53.
[98] R. Grol, J. Grimshaw, From best evidence to best practice: effective implementation of change in patients' care, Lancet 362(9391) (2003) 1225-30.
[99] J. Rycroft-Malone, The PARIHS framework--a framework for guiding the implementation of evidence-based practice, Journal of nursing care quality 19(4) (2004) 297-304.
[100] I.D. Graham, J. Logan, M.B. Harrison, S.E. Straus, J. Tetroe, W. Caswell, N. Robinson, Lost in knowledge translation: time for a map?, The Journal of continuing education in the health professions 26(1) (2006) 13-24.
[101] R. Grol, M. Wensing, What drives change? Barriers to and incentives for achieving evidence-based practice, The Medical journal of Australia 180(S6) (2004) S57-60.
[102] C. Lammens, V. Atema, V. Bouwman, M. Stouten-Kemperman, Opschalingsgids psychosociale oncologie: voor het vergroten van landelijke beschikbaarheid van psychosociale interventies, IKNL, 2019.

CHAPTER 8

# SUMMARY

## SUMMARY

As a result of breast cancer (BC) treatment, younger women are at risk for developing physical and mental health problems, including treatment-induced menopausal symptoms. Hot flushes and night sweats (HF/NS) are of particular concern due to the high prevalence rate and significant bother associated with them. Notwithstanding, these HF/NS cause some women to discontinue their endocrine treatment.

**Chapter 1** describes the need for effective treatment options to alleviate menopausal symptom burden for BC survivors with treatment-induced menopausal symptoms. Previous studies demonstrated that cognitive behavioral therapy (CBT) provided in a group setting results in significantly lower menopausal symptom burden among BC survivors. This traditional setting is, however, not without challenges and especially younger BC survivors reported scheduling conflicts leading to low compliance rates. In order to provide these women with an alternative, we investigated the efficacy of this CBT program provided via the Internet (iCBT).

The following three research questions are addressed in this thesis:

1. What is the efficacy of the iCBT program, with and without therapist support, in alleviating menopausal symptom burden, and other psychosocial outcomes in BC survivors with treatment-induced menopausal symptoms?
2. What is the cost-utility, cost-effectiveness and budget impact of the iCBT program, with and without therapist support, aimed at alleviating menopausal symptom burden in BC survivors with treatment-induced menopausal symptoms?
3. What are the moderators and mediators of the observed treatment effects in BC survivors with treatment-induced menopausal symptoms?

**Chapter 2** presents the results of our pilot study. We describe the development of the iCBT program, report on the experiences of a small group of BC survivors and therapists with the initial version of the guided iCBT program, and present preliminary efficacy data in terms of reducing menopausal symptom burden. We adapted a face-to-face CBT program developed by Hunter and colleagues, making it more suitable for online

administration. Results indicated that this guided iCBT program was well accepted and positively rated. In addition, compliance rates were high and the women reported a significant decrease in the perceived impact of HF/NS and overall levels of menopausal symptoms. The few suggestions based on qualitative input from the participants and therapists led to further refinement of the program.

**Chapter 3** describes, in detail, the rationale and design of the main study, evaluating the efficacy of the iCBT program, with and without therapist support, in alleviating menopausal symptom burden, and other psychosocial outcomes in BC survivors with treatment-induced menopausal symptoms. Participants were recruited from 12 community and academic hospitals. Eligible women were randomly allocated to a guided iCBT, self-managed iCBT or a control group. Women allocated to the iCBT groups had access to a 6-week program. This program was primarily focused on HF/NS, but stress-management and sleep difficulties were also addressed. Women in the guided iCBT group received an additional intake by telephone and weekly online feedback from a trained psychologist or medical social worker. We administered a comprehensive set of questionnaires at baseline, 10 weeks and 24 weeks post-randomization. Primary outcomes included the perceived impact of HF/NS and overall levels of menopausal symptoms. Sleep quality, sexual functioning, frequency of HF/NS, psychological distress and health-related quality of life served as secondary outcomes.

**Chapter 4** presents the results of our randomized controlled trial (RCT) of the efficacy of iCBT, with and without therapist support, in alleviating menopausal symptom burden and other psychosocial outcomes in BC survivors with treatment-induced menopausal symptoms. In total, 254 women participated in the study. They were, on average, 47 years of age and the average time since diagnosis was 3 years. Compliance rates were high, especially for the three core modules of the program (91% and 79% for the guided and self-managed iCBT groups, respectively). Compared to women in the control group, women in the guided and self-managed iCBT groups reported a significantly greater decrease in the perceived impact of HF/NS and improvement in sleep quality. The guided group also reported a significant decrease in overall levels of menopausal symptoms and night sweats frequency when compared to the control group. At longer-term follow-up, the effects remained significant but with smaller effect sizes.

Additional longer-term results for both intervention groups demonstrated a significant reduction in hot flush frequency. At the individual patient level, more women in the guided and self-managed iCBT groups showed a clinically significant improvement than women in control group in perceived impact of HF/NS (43%, 35% and 18%, respectively) and overall levels of menopausal symptoms (44%, 31%, 23%, respectively). Comparable percentages were observed at longer-term follow-up. We did not observe significant treatment effects for sexual functioning, psychological distress or health-related quality of life.

**Chapter 5** presents the results of the cost-utility, cost-effectiveness and budget impact analyses for both iCBT formats, i.e. with and without therapist support, compared to the control group. Cost-utility ratios were € 23,331 per 'quality-adjusted life year' (QALY) and € 11,277 per QALY for the guided and self-managed iCBT, respectively. This is well below the generally accepted threshold of € 30.000 / QALY. For the guided and self-managed iCBT a clinically significant reduction in menopausal symptom burden required incremental costs of approximately € 1500 and € 625, respectively. Lastly, an annual budget impact of € 192.990 and € 74.592 was estimated for the guided and self-managed iCBT, respectively, which is low compared to the budget impact of the medical treatment of BC. When comparing the results of both formats of the iCBT program, all three types of economic evaluations tended to favor the self-managed iCBT over the guided iCBT.

**Chapter 6** reports on patient characteristics that moderate and therapeutic change mechanisms that mediate treatment effects. Results indicated that educational level, but not age, time since diagnosis, current endocrine treatment, oophorectomy, frequency of HF/NS or psychological distress, moderate the treatment effects. Women with a high school or vocational degree benefited more from the iCBT program than women with college or university degrees. Women in the iCBT groups developed healthier beliefs about experiencing hot flushes in public, the impact of night sweats on sleep and about the ability to control and cope with hot flushes, than women in the control group. The development of healthier beliefs mediated treatment effects. The acquisition of behavioral coping strategies and decreased psychological distress did not mediate treatment effects.

**Chapter 7** discusses the main findings of this thesis, including the

methodological limitations pertaining to the design of the study, nature and quality of assessments and the iCBT program, and provides food for thought. In conclusion, our iCBT program, provided with and without therapist support, resulted in lower menopausal symptom burden, increased sleep quality and decreased frequency of HF/NS. In addition, results from the economic evaluation demonstrate that both formats can be considered cost-effective. We would, therefore, recommend the implementation of this program in regular clinical care. We believe that future efforts should be directed towards the uptake of Internet-based interventions in clinical care. We propose three processes that could facilitate this, by 1] rapid user-centered development, testing and evaluation of iCBT programs, 2] integrating Internet-based programs in order to, if needed, address a variety of problems, and 3] addressing nationwide preconditions for clinical uptake as early as possible, preferably during the development phase of an intervention.

# SAMENVATTING
## (SUMMARY IN DUTCH)

Als gevolg van de behandeling voor borstkanker hebben jonge vrouwen een verhoogd risico op fysieke en mentale klachten waaronder vroegtijdige overgangsklachten. Opvliegers en nachtzweten zijn de vaakst voorkomende overgangsklachten. In **Hoofdstuk 1** beschrijven we de relatie tussen de behandeling van borstkanker en het ontstaan van vroegtijdige overgangsklachten. Opvliegers kunnen de kwaliteit van leven van deze vrouwen negatief beïnvloeden. Ook zijn er vrouwen die door de ervaren last, ervoor kiezen om de anti-hormonale behandeling af te breken. De noodzaak voor een laagdrempelige effectieve behandeling van deze klachten is daarom hoog. In dit hoofdstuk geven we inzicht in de bestaande medische en niet-medische behandelingen gericht op het afnemen en/of verlichten van met name opvliegers.

Een veelbelovende therapeutische behandeling, waarvoor meerdere (inter) nationale studies de werkzaamheid hebben aangetoond, betreft cognitieve gedragstherapie (CGT). Deze therapie, gegeven als groepstherapie, resulteerde in een sterke verlichting van de overgangsklachten. Het bleek, echter, lastig voor jonge vrouwen om deze groepssessies bij te wonen. Om deze vrouwen toch de juiste zorg te kunnen bieden, hebben we het CGT programma vertaald naar een Internet format (hierna iCGT genoemd). In het huidige proefschrift staan de werkzaamheid en de kosteneffectiviteit van deze therapeutische behandeling centraal en beantwoorden we de volgende onderzoeksvragen:

1. Wat is het effect van iCGT, aangeboden met en zonder professionele begeleiding, op het verlichten van overgangsklachten en andere psychosociale problemen van vrouwen die door de behandeling voor borstkanker vervroegd in de overgang zijn gekomen?
2. Wat is de kosten-utiliteit, kosteneffectiviteit en budget impact van iCGT, aangeboden met en zonder professionele begeleiding, op het verlichten van overgangsklachten van vrouwen die door de behandeling voor borstkanker vervroegd in de overgang zijn gekomen?
3. Welke factoren modereren en welke werkmechanismen mediëren de effecten van de iCGT bij vrouwen die door de behandeling voor borstkanker vervroegd in de overgang zijn gekomen?

In **Hoofdstuk 2** wordt de ontwikkeling van het iCGT programma beschreven en de uitkomsten van een kleinschalige pilot studie naar de werkzaamheid van het programma gepresenteerd. Tevens wordt de tevredenheid van deelnemers met het iCGT programma, aangeboden onder begeleiding van medisch maatschappelijk werkers, en de ervaringen van deze professionals besproken. Het iCGT programma is gebaseerd op een bestaand face-to-face programma en met enige aanpassingen geschikt gemaakt voor aanbieding via het Internet. De deelneemsters waren erg tevreden over het programma en de begeleiding. De meeste vrouwen hebben het gehele programma doorlopen en ervaarden een verlichting van opvliegers en andere overgangsklachten. Zowel de deelneemsters als de begeleiders hebben enkele suggesties ter verbetering benoemd, welke hebben geleid tot een doorontwikkeling van het programma.

Hierop volgend hebben we een grootschalige studie opgezet om deze iCGT te evalueren. Dit beschrijven we in **hoofdstuk 3**. We beschrijven de aanleiding en opzet van deze gerandomiseerde gecontroleerde studie waarin we de werkzaamheid van iCGT, aangeboden met en zonder professionele begeleiding, in het verlichten van overgangsklachten bij vrouwen die door de behandeling van borstkanker vroegtijdig in de overgang zijn gekomen. Uit twaalf ziekenhuizen in Nederland werden (ex)borstkankerpatiënten uitgenodigd voor deelname. De deelnemende vrouwen werden middels loting toegewezen aan een begeleide iCGT groep, een onbegeleide iCGT groep of een wachtlijst-controlegroep. Vrouwen die het programma volgden, met of zonder professionele begeleiding, kregen toegang tot het 6 weken durende iCGT programma. De nadruk binnen het programma lag op de ervaren opvliegers, maar andere aandachtsgebieden, zoals stress-management en slaap problematiek, kwamen ook aan bod. De vrouwen in de begeleide iCGT groep kregen daarnaast ook een telefonisch kennismakingsgesprek met een begeleider. Deze begeleider gaf daarna wekelijkse online feedback op hun voortgang. Alle vrouwen werden verzocht om op drie momenten, namelijk voor de start van de studie, na 10 weken en 24 weken na de randomisatie een set aan vragenlijsten in te vullen. De primaire uitkomstmaten waren een verlichting van de ernst van opvliegers en van andere overgangsklachten. De overige uitkomstmaten betroffen de kwaliteit van slaap, seksueel functioneren, frequentie van opvliegers, psychische distress en gezondheids-gerelateerde kwaliteit van leven.

In **Hoofdstuk 4** worden de resultaten met betrekking tot de effectiviteit van iCGT, met en zonder professionele begeleiding, in het verlichten van overgangsklachten en andere klachten bij vrouwen die door de behandeling van borstkanker vroegtijdig in de overgang zijn gekomen, gepresenteerd. Er deden in totaal 254 vrouwen mee aan de studie. De gemiddelde leeftijd was 47 jaar en er was gemiddeld drie jaar verstreken sinds de borstkanker diagnose. Een meerderheid van de vrouwen in de begeleide en onbegeleide iCGT groep heeft het gehele programma doorlopen. Op de korte termijn en vergeleken met de vrouwen in de controlegroep, rapporteerden de vrouwen in beide iCGT groepen een sterkere verlichting van opvliegers en een betere kwaliteit van slaap. Daarnaast rapporteerden de vrouwen in de begeleide iCGT groep ook een verlichting van andere overgangsklachten en minder nachtelijke opvliegers. Op lange termijn bleven de uitkomsten nagenoeg gelijk. Op deze termijn hadden de vrouwen in de iCGT groepen ook minder opvliegers dan vrouwen in de controlegroep. Meer vrouwen in de begeleide en onbegeleide iCGT groepen ervaarden een klinisch significante verbetering van klachten dan vrouwen in de controlegroep, m.b.t. verlichting van opvliegers (43%, 35%, 17.5% respectievelijk) en overige overgangsklachten (44%, 31%, 23% respectievelijk). Deze percentages bleven nagenoeg gelijk op de lange termijn. Er werd geen significant verschil tussen de iCGT groepen en de controlegroep waargenomen voor seksueel functioneren, psychische distress en gezondheids-gerelateerde kwaliteit van leven.

In **Hoofdstuk 5** worden de uitkomsten van de economische evaluatie gepresenteerd. Hiervoor werden een kosten-utiliteit, kosteneffectiviteit en budget impact analyse uitgevoerd. De kosten-utiliteiten ratio's waren € 23.331 / 'quality adjusted life year' (QALY) en € 11.277 / QALY voor de begeleide en onbegeleide iCGT respectievelijk. Beide bedragen zijn lager dan het veelal aangehouden maximum van € 30.000 / QALY. Een klinisch significante verlichting van overgangsklachten ging gepaard met incrementele kosten van gemiddeld € 1.500 voor de begeleide en € 625 voor de onbegeleide iCGT. De jaarlijkse budget impact werd geschat op € 192.990 en € 74.592 voor de begeleide en onbegeleide iCGT respectievelijk. Dit is in vergelijking met de budget impact van medische behandelingen voor kanker triviaal. De resultaten van alle drie de analyses wijzen op een betere verhouding tussen de kosten en de werkzaamheid voor de onbegeleide iCGT dan voor de begeleide iCGT.

In **Hoofdstuk 6** wordt er dieper ingegaan op de vraag welke vrouwen het meeste baat hebben bij het volgen van het iCGT programma en welke werkmechanismen bijdragen aan het positieve effect van het programma. Uit de resultaten blijkt dat opleidingsniveau, maar niet leeftijd, tijd sinds diagnose, een eierstokverwijdering, huidige anti-hormonale therapie, de frequentie van opvliegers en psychische distress, het effect van iCGT modereren. Vrouwen die de middelbare school of middelbaar beroepsonderwijs hebben afgerond hebben meer baat bij het iCGT programma dan vrouwen die HBO of universiteit hebben afgerond. In vergelijking met de controlegroep, leidde het volgen van iCGT tot gezondere overtuigingen over het ervaren van opvliegers in het bijzijn van anderen, de impact van nachtelijke opvliegers op slaap en overtuigingen m.b.t. controle en omgang met opvliegers. Deze verbeterde overtuigingen droegen bij aan het positieve effect van de iCGT. De iCGT leidde ook tot gedragsveranderingen, deze droegen echter niet significant bij aan het behandel-effect.

In **Hoofdstuk 7** worden de belangrijkste bevindingen en de methodologische overwegingen m.b.t. het design van de studie, de aard en kwaliteit van de metingen en het iCGT programma beschreven. Tot slot volgt er een drietal aanbevelingen om de nationale implementatie van het huidige en soortgelijke programma's te bespoedigen. Alles bij elkaar genomen komen we tot de conclusie dat iCGT, aangeboden met en zonder professionele begeleiding, resulteerde in een verlichting van opvliegers en andere overgangsklachten, een verbeterde kwaliteit van slaap en een vermindering van het aantal opvliegers, zowel overdag als 's nachts. Daarnaast blijkt het programma kosteneffectief. Dit alles pleit voor opname in het reguliere zorgaanbod voor vrouwen die door de behandeling van borstkanker vervroegd in de overgang zijn gekomen. Om implementatie te bespoedigen, onderschrijven wij in dit hoofdstuk het belang van een user-centered design en identificatie van een set van karakteristieken die de werkzaamheid van een programma via het Internet vergroten, zodat er niet herhaaldelijk grootschalige studies uitgevoerd hoeven te worden. Daarnaast adviseren wij om bestaande programma's te integreren, zodat er, indien gewenst, een groter scala aan problemen geadresseerd kan worden. Hiermee is het ook waarschijnlijk dat er efficiënter gebruik gemaakt wordt van (financiële) middelen. Afsluitend, onderstrepen wij het belang van samenwerking tussen experts op het gebied van onderzoek, praktijk en organisatie van zorg, zodat er tijdig aandacht is voor randvoorwaarden die uitzicht op succesvolle landelijke beschikbaarheid van evidence-based interventies vergroten.

# APPENDICES

A

# ABBREVIATIONS

| | |
|---|---|
| ANOVA | Analysis of variance |
| ARR | Absolute risk ratio |
| BC | Breast cancer |
| BIA | Budget impact analysis |
| CAM | Complementary alternative medicine |
| CBT | Cognitive behavioral therapy |
| CE | Cost-effectiveness |
| CEA | Cost-effectiveness analysis |
| CEAC(s) | Cost-effectiveness acceptability curve(s) |
| CONSORT | Consolidated standards of reporting trials |
| EQ-5D | EuroQol 5 dimensions questionnaire |
| ES | Effect Size |
| FACT-ES | Functional assessment of cancer therapy questionnaire – endocrine symptoms |
| GSE | General self-efficacy |
| GSQS | Groningen sleep quality scale |
| HADS | Hospital anxiety and depression scale |
| HF/NS | Hot flushes / night sweats |
| HFRS | Hot flush rating scale |
| HRQOL | Health related quality of life |
| HRT | Hormone replacement therapy |
| iCBT | Internet-based cognitive behavioral therapy |
| ICUR(s) | Incremental cost-utility ratio(s) |
| IMCQ | Imta medical consumption questionnaire |
| IRB | Institutional review board |
| ITT | Intention to treat |
| MOS-SS | Medical outcome study – social support scale |
| MR | Mortality rate |
| N | Number |
| NNT | Number needed to treat |
| PP | Per- protocol |
| PSA | Probabilistic sensitivity analysis |
| QALY | Quality adjusted life year |
| RCT(s) | Randomized controlled trial(s) |
| REML | Restricted maximum likelihood |

| | |
|---|---|
| SAQ | Sexual activity questionnaire |
| SD | Standard deviation |
| SE | Standard error |
| SF-36 | Medical outcome study – 36 item – short form |
| SF-6-D | Medical outcome study – 6 dimensions |
| SSRI'S | Selective serotonin reuptake inhibitors |
| T0 | Baseline assessment |
| T1 | Short-term follow-up assessment |
| T2 | Longer -term follow-up assessment |
| WHO | World Health Organisation |
| WLC | Waiting list control group |
| WTP | Willingness-to-pay |

# AUTHORS' CONTRIBUTIONS

Neil K. Aaronson was the principal investigator and Marieke van Leeuwen, Hester S.A. Oldenburg and Marc van Beurden were the co-principal investigators of this study. Vera Atema was the PhD candidate on this study. Myra Hunter played a key role in the development of the Internet-based cognitive behavioral therapy program.

## Chapter 2

V. Atema, M. van Leeuwen, H.S.A. Oldenburg, M. van Beurden, M.S. Hunter, N.K. Aaronson, An Internet-based cognitive behavioral therapy for treatment-induced menopausal symptoms in breast cancer survivors: results of a pilot study, Menopause 24(7) (2017) 762-767.

**Conception and design:** Vera Atema, Marieke van Leeuwen, Hester S.A. Oldenburg, Marc van Beurden, Myra S. Hunter and Neil K. Aaronson.
**Collection of data:** Marieke van Leeuwen
**Data analysis:** Vera Atema
**Interpretation of the data and writing of the manuscript:** Vera Atema, Marieke van Leeuwen, Hester S.A. Oldenburg, Marc van Beurden, Myra S. Hunter and Neil K. Aaronson.
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## Chapter 3

V. Atema, M. van Leeuwen, H.S. Oldenburg, V. Retel, M. van Beurden, M.S. Hunter, N.K. Aaronson, Design of a randomized controlled trial of Internet-based cognitive behavioral therapy for treatment-induced menopausal symptoms in breast cancer survivors, BMC Cancer 16(1) (2016) 920.

**Conception and design:** Vera Atema, Marieke van Leeuwen, Hester S.A. Oldenburg, Valesca P. Retel, Marc van Beurden, Myra S. Hunter and Neil K. Aaronson.
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## Chapter 4

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**Conception and design:** Vera Atema, Marieke van Leeuwen, Hester S.A. Oldenburg, Marc van Beurden, Myra S. Hunter and Neil K. Aaronson.
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## Chapter 5

J.G.E. Verbeek*, V. Atema*, J.C. Mewes, M. van Leeuwen, H.S.A. Oldenburg, M. van Beurden, M.S. Hunter, W.H. van Harten, N.K. Aaronson, V.P. Retel, Cost-utility, cost-effectiveness, and budget impact of Internet-based cognitive behavioral therapy for breast cancer survivors with treatment-induced menopausal symptoms, Breast Cancer Res Treat 178(3) (2019) 573-585.
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**Conception and design:** Joost G.E. Verbeek, Vera Atema, Janne C. Mewes, Marieke van Leeuwen, Hester S.A. Oldenburg, Marc van Beurden, Myra S. Hunter, Wim H. van Harten, Neil K. Aaronson and Valesca P. Retel.
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## Chapter 6

V. Atema, M. van Leeuwen, J.M. Kieffer, H.S. Oldenburg, M. van Beurden, M.S. Hunter, N.K. Aaronson, Internet-based cognitive behavioral therapy aimed at alleviating treatment-induced menopausal symptoms in breast cancer survivors: moderators and mediators of treatment effects, Maturitas Epub ahead of print (2019).

**Conception and design:** Vera Atema, Marieke van Leeuwen, Jacobien M. Kieffer, Hester S.A. Oldenburg, Marc van Beurden, Myra S. Hunter and Neil K. Aaronson.
**Collection of data:** Vera Atema, Hester S.A. Oldenburg, Miranda A. Gerritsma, Marianne A Kuenen, Peter W. Plaisier, Alexander M.F. Lopes Cardozo, Yvonne E.A. van Riet, Gijsbert Heuff, Herman Rijna, Suzan van der Meij, Eva M. Noorda, Gert Jan Timmers, Bart C. Vrouenraets, Matthe Bollen, Henk van der Veen and Nina Bijker.
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*– J.F. Kennedy*

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## ABOUT THE AUTHOR

Vera Atema was born in Barneveld on February 13th,1985. She studied Psychology at the University of Leiden. During this time she spent nearly a year in Africa, either travelling or evaluating a sexual health program for her master thesis. It became apparent that Vera was very passionate about improving quality of life for those in need. Graduating her master Health Psychology, cum laude, in 2009 launched her professional career. Subsequently she explored different fields of work and held several positions as researcher, academic teacher and counsellor. In 2015 she started her PhD research at the Netherlands Cancer Institute. Her research focused on alleviating hot flushes and night sweats in breast cancer survivors with treatment-induced menopausal symptoms. During this time she became actively involved in the 'Nederlandse Vereniging voor Psychosociale Oncologie'. Currently she works at the Netherlands Comprehensce Cancer Organisation (IKNL), continuing her efforts to impact psychosocial healthcare for cancer patients and survivors.