Internet-based cognitive behavioral therapy for sexual dysfunctions after breast cancer

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General discussion
In the previous chapters we reported on the outcomes of a randomized controlled trial (RCT) of Internet-based cognitive behavioral therapy (CBT) in breast cancer survivors with a sexual dysfunction according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV\textsuperscript{1}). We described patient-related and clinical factors associated with the women's DSM-IV sexual dysfunctions and their sexual functioning and distress, and the association between the sexual functioning of breast cancer survivors and their partners. We reported on the short- and long-term efficacy of the Internet-based CBT program in improving the sexual functioning of the women as well as that of their partners. We not only evaluated changes in the women's sexual functioning, but also in their level of sexual distress, relationship intimacy, marital functioning, body image, menopausal symptoms, psychological distress and health-related quality of life (HRQL). We also investigated predictors of a successful outcome of the therapy in terms of the breast cancer survivors’ sexual functioning and distress levels. This chapter discusses the study results, methodological considerations and implications for further research.

**MAIN FINDINGS**

Although many women experience sexual problems after the treatment of breast cancer (BC)\textsuperscript{2,3}, little is known about BC survivors with a diagnosis of sexual dysfunction according to the criteria of the DSM-IV\textsuperscript{1}. The baseline data that were collected as part of our RCT provide insight into the sexual functioning of this specific group of women. The most prevalent sexual dysfunctions for which the women in our sample received a diagnosis were hypoactive sexual desire disorder (83%), sexual arousal disorder (40%) and dyspareunia (33%) (Chapter 3). Women who had been treated with endocrine therapy were more often diagnosed with hypoactive sexual desire disorder (HSDD), and women treated with immunotherapy more often with dyspareunia. In line with research in the general population\textsuperscript{4}, older age was associated with less sexual distress.

Not only the BC survivors’ sexual functioning, but also that of their partners was affected, which was reflected in the large proportion (55%) of the male partners that reported moderate or severe erectile dysfunction (Chapter 3). This finding is consistent with findings of previous studies\textsuperscript{5,6}, and underscores that it is important for health care professionals to involve both partners in the discussion about sexuality after BC, and especially - if applicable - in subsequent sex therapy. The effect of the women's BC treatment on the partner was also reflected in the finding that partners of women who had undergone breast reconstruction reported better orgasmic and overall sexual functioning than partners of women who had received breast-conserving therapy. Although both the BC survivors and their partners reported low levels of sexual functioning, we identified few
correlations between the self-reported sexual functioning of the women and that of their partners.

The Internet-based CBT program improved women’s overall sexual functioning, sexual desire, sexual arousal, vaginal lubrication, sexual pleasure, and resulted in less discomfort during sex (i.e., vaginal dryness and penetration-related pain) and less sexual distress (Chapter 4). Women also reported an improved body image. No changes were observed at post-CBT for orgasmic functioning, sexual satisfaction, frequency of sexual activity, relationship intimacy, marital functioning, menopausal symptoms, psychological distress, or health-related quality of life. During the nine-month follow-up period, all improvements were maintained, except for sexual pleasure, which decreased – although not to baseline levels. Body image improved even further during follow-up (Chapter 5).

An evaluation of the predictors of therapy success indicated that better post-CBT sexual functioning was associated with better baseline female sexual functioning, better baseline sexual functioning of the partner and higher therapy compliance. Predictors of lower post-CBT sexual distress included lower baseline sexual distress, better baseline female sexual functioning, higher baseline relationship satisfaction of the partner and higher therapy compliance (Chapter 6). Therapy compliance, in turn, was predicted by the active involvement of the partner in therapy and a better therapeutic relationship. The baseline levels of sexual functioning and distress were, however, not predictive of the effectiveness of the Internet-based CBT; they were only predictive of the level of sexual functioning and distress over time (e.g., women with better baseline sexual functioning also had better post-CBT sexual functioning). The specific components of BC treatment were not predictive of post-intervention sexual functioning. The findings suggest that any BC survivor, regardless of her baseline level of sexual functioning or distress or her specific BC treatment, may benefit from Internet-based CBT for sexual dysfunction. We recommended that, to enhance compliance with and the effectiveness of the CBT program, particular attention be paid to the therapeutic relationship and to the involvement of the partner in therapy.

The Internet-based CBT program had a sustained, positive effect on the partners’ overall sexual satisfaction, sexual intimacy and sexual relationship satisfaction (Chapter 7). Although the partners’ overall sexual functioning, orgasmic functioning and intercourse satisfaction improved during the Internet-based CBT, these effects were not maintained after a nine-month follow-up period.

**BC treatment and sexual functioning**

To our knowledge, our study is the first to evaluate the association between specific BC treatment features and specific DSM-IV sexual dysfunctions (Chapter 3). The finding that endocrine therapy was associated with HSDD is consistent with previous research that has shown that endocrine therapy negatively affects sexual functioning\(^7^8\), but also suggests that endocrine treatment is a specific risk factor for the development of HSDD. The
negative influence of endocrine treatment on the effect and production of estrogens and androgens might be an explanation for this association, as a decrease in sex steroid hormones is one of the factors in the multifactorial etiology of decreased sexual desire\(^9\). The underlying mechanism for the association between endocrine treatment and this specific DSM-IV sexual dysfunction warrants further research.

The association between immunotherapy and dyspareunia might be explained by the potential relationship between immunotherapy and menopausal symptoms, including vaginal dryness, which was reported in a previous study\(^10\). However, another study did not observe an increased likelihood of amenorrhea in patients receiving trastuzumab\(^11\). As both studies included a small number of patients treated with immunotherapy, more research into the relationship between immunotherapy and menopausal symptoms is required.

**Association between BC survivors’ and their partners’ sexual functioning**

We detected fewer correlations between the sexual functioning of BC survivors and their partners (Chapter 3) than reported by studies in a non-clinical sample\(^12\) and in a prostate cancer sample\(^13\), in which most areas of the couples’ sexual functioning were found to be correlated, albeit only moderately so in the non-clinical sample (i.e., ranging from \(r = .08 \) to \(.46\))\(^12\). This might be explained, at least in part, by differences between male and female sexual functioning, such as men reporting higher sexual desire than women\(^14\), the gender differences in the degree of concordance between the perception of genital response and actual genital sexual arousal\(^15\), and differences in orgasm frequency\(^16,17\). The correlations reported by Badr et al.\(^13\) were stronger (\(r = .30-.80\)). It seems, however, that Badr et al.\(^13\) did not exclude couples from the analysis that were sexually inactive. This may have influenced the findings, as both questionnaires used in the analysis assign a score of zero to the response option ‘no sexual activity’. When sexually inactive couples are included in the correlation analysis and both partners select this option, this may increase the possibility of finding a (larger) correlation.

Partners of women who underwent breast reconstruction (BR) reported better orgasmic functioning and overall sexual functioning than partners of women who had undergone breast-conserving treatment (BCT) (Chapter 3). A possible explanation could be that a BR might result in a better body image than does BCT, with subsequent positive effects on the woman’s as well as on her partner’s sexual functioning. However, we did not observe a significant association between surgical procedure and women’s body image. Another explanation might be that male partners experience a reconstructed breast as more sexually attractive than a conserved breast, resulting in higher levels of overall sexual functioning and orgasmic functioning.
Efficacy of the intervention

Breast cancer survivors

We observed improvements in multiple areas of BC survivors’ sexual functioning after undergoing Internet-based CBT (Chapter 4 and 5). This was not unexpected, as the majority of women were diagnosed with two sexual dysfunctions (Chapter 3 and 4) and thus there was ample room for improvement in several areas of sexual functioning. This finding is in line with research demonstrating that many sexually dysfunctional women are diagnosed with multiple sexual dysfunctions18. Our findings regarding the efficacy of the Internet-based CBT are similar to those of a previous study of a 10-week Internet-based CBT program for sexual dysfunction in women in the general population19. In this latter study, sexually dysfunctional women reported improved sexual and relationship functioning immediately following CBT, as well as 3 months post-CBT. We would point out that the post-treatment level of sexual functioning of our study sample was lower than that of women in the trial of Jones and McCabe19. This might suggest that our intervention was less effective in improving sexual functioning. However, this difference might be explained, in part, by the fact that we included BC survivors who had a DSM-IV diagnosis of sexual dysfunction, while the recruitment of women to the trial of Jones and McCabe19 was based on self-reported sexual problems. Another possible explanation is that, for their analyses of the effect of the CBT program, Jones and McCabe19 included only the women who indicated that they were sexually active at baseline. In our opinion, this approach limits the generalizability of the results, as only the better functioning subgroup of the study sample is evaluated. The difference in the baseline and post-CBT FSFI scores between the two studies could also be indicative of the extent to which the sexual functioning of BC survivors is affected by BC diagnosis and treatment. This idea is supported by the fact that most baseline FSFI scores of our BC survivors were lower (indicating a lower level of sexual functioning) than those of a group of Dutch women with sexual problems who sought professional help20. Interestingly, the post-treatment sexual functioning of the women in the trial of Jones and McCabe19 was still lower than that of healthy women20, suggesting that it is challenging for women with sexual problems to achieve a level of sexual functioning that is equal to that of healthy women, even with the help of therapy. This is possibly even more so for BC survivors, given the effects of BC treatment on both the emotional and physical aspects of sexual functioning. This suggests that the aim of interventions targeting the sexual functioning of BC survivors should not necessarily be to return to the levels of sexual functioning experienced before the diagnosis of cancer, but rather to support women in adjusting to their altered body and sexuality after BC.

Although the Internet-based CBT realized long-term improvement in the sexual functioning of BC survivors, some loss of treatment gains (although not statistically significant) was observed in most areas during follow-up (Chapter 5). A similar loss of treatment gains
during follow-up was reported by Jones and McCabe\textsuperscript{19}. It may be that, after completion of the CBT, the loss of therapist encouragement to engage in sex may result in some loss of effect. The recent developments in eHealth may offer possibilities for post-therapy support, for example, by integrating a smartphone application into the therapy program that provides continuing support, that can be used to reinforce the lessons learned in therapy, to provide additional homework exercises, and to strengthen the relapse prevention elements that are often part of such CBT programs.

In our trial, we did not observe any significant improvement over time in women’s sexual satisfaction (Chapter 4 and 5). This is surprising in that the mean baseline scores of the FSFI satisfaction subscale indicated that there was ample room for improvement in this area. A possible explanation for the lack of improvement might be that the items in this subscale primarily assess a woman’s satisfaction with her sexual relationship with her partner. Consequently, a woman’s response to these questions might not only be a reflection of her own sexual satisfaction, but possibly also of her assumptions about the sexual satisfaction of her partner\textsuperscript{21}, something that women may feel uncertain about. Also, it is important to note that most women in our sample (87.6\%) developed sexual problems during or after the BC treatment, reflecting a rather abrupt change in sexual health. While many women’s sexual functioning improved as a result of therapy, it may not have returned to pre-BC levels (something that we were not able to measure). Yet, women may have rated their satisfaction with their sex lives in relation to their pre-BC situation, rather than to their situation just prior to entering CBT program.

We would note that, as a result of the correction for multiple testing (i.e., use of a more stringent $p$ value, set at 0.01 rather than 0.05), a number of outcomes were labeled as being statistically non-significant, while in fact there appeared to be a trend toward improvement from baseline to immediate post-intervention. This was the case for orgasmic functioning, frequency of sexual activity, social intimacy, recreational intimacy and sexual relationship satisfaction (Chapter 4). The fact that orgasmic functioning improved to a lesser extent than sexual desire and arousal might be explained by the fact that, although sexual desire and arousal are a prerequisite to achieving an orgasm, an improvement in desire and/or arousal does not necessarily result in an equally large improvement in orgasmic functioning. The fact that, in general, many women experience problems in achieving an orgasm\textsuperscript{22}, most likely as a result of insufficient clitoral stimulation during sexual activity\textsuperscript{23}, might be an additional explanation for the smaller improvement observed in orgasmic functioning. Expanding our treatment program with specific communication exercises to coach women in verbalizing their sexual preferences to their partner, especially with regard to clitoral stimulation, may therefore have improved the women’s orgasmic functioning to a greater extent.

The Internet-based CBT realized a long-term improvement in vaginal lubrication during sexual activity (Chapter 4 and 5). This finding is somewhat unexpected in that postmeno-
pausal women often experience vaginal dryness\textsuperscript{24}, and that BC treatment (particularly chemotherapy and endocrine therapy) induces menopause in premenopausal women, and can exacerbate menopausal symptoms, including vaginal dryness and atrophy, in women who were already post-menopausal\textsuperscript{25}. Healthy postmenopausal women who experience vaginal dryness can use hormone replacement therapy (HRT)\textsuperscript{26,27}. However, the use of HRT is contraindicated in BC survivors\textsuperscript{28}, as approximately 80\% of breast cancers are estrogen/progesterone positive\textsuperscript{29}. The fact that our study sample, despite the inability to use hormone supplementation, reported improved vaginal lubrication after Internet-based CBT is in line with previous research\textsuperscript{30} demonstrating that, although postmenopausal women experience more vaginal dryness than premenopausal women in a non-aroused state, this difference is no longer present with sufficient erotic stimulation. Vaginal dryness and dyspareunia in postmenopausal women are therefore probably not the result of a physical inability to self-lubricate, but rather seem to reflect a problem with sexual arousal\textsuperscript{30}. The fact that women in our study reported a sustained improvement in vaginal lubrication during sexual activity may indicate that the Internet-based CBT was successful in teaching women and their partners effective ways to achieve sexual stimulation.

Women in the CBT group reported a decrease in discomfort during sex (Sexual Activity Questionnaire (SAQ) discomfort scale), but no change in levels of pain during sex (FSFI pain subscale) (Chapter 4). Whereas the FSFI subscale assesses the frequency and degree of pain in the context of vaginal penetration, the SAQ subscale also includes the degree of vaginal dryness during sexual activity; an aspect of sexual functioning that improved as a result of the Internet-based CBT. This might explain these seemingly contradictory findings. Another explanation might be that, despite improvement in vaginal lubrication during sex, the degree of vaginal atrophy remained unchanged due to decreased estrogen levels, causing pain during vaginal penetration.

**Partners**

Although the partners of women in the intervention group reported a sustained improvement in overall sexual satisfaction, sexual intimacy and sexual relationship satisfaction, our intervention did not realize a sustained improvement in other areas of the partners’ sexual functioning. As indicated previously in Chapter 7, this finding was not surprising, as the intervention focused mainly on the sexual functioning of the BC survivors. However, the fact that the scores on the International Index of Erectile Function (IIEF) of our partner sample were significantly lower than those of a healthy population\textsuperscript{31} suggests that there was room for improvement in the partners’ sexual functioning. It may therefore be important to not only encourage the partners to participate in therapy, but to consider it as an integral element of the therapy as is often the case in face-to-face sex therapy, in which the partner is present during the therapy sessions. More active involvement of the partner enables therapists to obtain a better picture of the partner’s functioning and to use
partner-specific interventions, if necessary. Our CBT program did contain a module that specifically targeted the sexual functioning of male partners, including psycho-education and exercises. However, the content of this module was apparently not sufficient to realize sustained improvements. Future programs should therefore include more psycho-educational information and exercises targeted at male sexual dysfunctions.

Greater partner involvement could also facilitate the therapist in carrying out a more thorough evaluation of potential relationship patterns underlying the sexual problems, since couples with sexual problems often have more dysfunctional conflict-resolution styles than healthy couples; this can be either a cause or an effect of sexual problems32. Although an exclusion criterion of our study was the presence of severe relationship problems, this does not necessarily mean that there were no dysfunctional dyadic coping or communication styles that may have negatively affected the couple’s sexual functioning.

METHODOLOGICAL CONSIDERATIONS

Our study had a number of methodological strengths, including the randomized controlled design, a large sample size, multicenter participation, the relatively long follow-up period of nine months, and the collection of data from partners of the BC survivors. However, the study also has some methodological limitations relating to the content and form of the CBT, the design of the study, the nature and quality of the assessments and to issues of cost-effectiveness.

Form and content of the CBT

Innovations in eHealth

Internet-based interventions have been demonstrated to be a feasible and effective treatment approach for a wide range of psychological disorders33,34. Since 2012, the year in which we conducted the pilot study that preceded our RCT, many innovations have taken place in the field of eHealth, with online programs becoming more interactive (e.g., through the use of animation, videos and feedback via smartphone applications or wearables). Conducting a clinical trial is a time-consuming activity. It is not uncommon for a trial to span a period of 7 years from applying for research funding to publishing the results35. Thus it is almost inevitable that new approaches and technologies emerge during the course of a clinical trial that would have been useful if available earlier on.

In the light of the current state of the art of eHealth, our intervention is in need of significant revision, as it consists primarily of written text supported by still images. A revised version of the program could include videos in which sexologists provide psycho-education and explain accompanying exercises, or psycho-educational animation videos about, for
example, genital anatomy and stimulation. Audio-guided sensate focus or relaxation exercises could be incorporated into the program, and availability and use could be enhanced by providing the exercises via a smartphone application. A smartphone application also enables the use of persuasive technology, which can be described as ‘computerized software or information systems designed to reinforce, change or shape attitudes or behaviors or both without using coercion or deception’. Fleming et al. recommend the use of persuasive technology in Internet interventions, such as notifications via smartphone or email, continued feedback regarding a patient’s therapy progress, use of a scheduling application for completion of next week’s intervention with a reminder service, and messages throughout the program regarding the benefits of following the program on a regular basis. Furthermore, Fleming et al. propose the use of serious gaming in eHealth interventions for the purpose of education and improving therapy adherence. An example of the use of serious gaming in sex therapy can be found in a recently developed online psychosexual educational program that uses “touchable” videos of virtual vulvas. The videos enable users of the program to familiarize themselves with the different techniques for clitoral stimulation that are explained in the program. In the development of the program, 1055 women were queried about location, pressure, shapes and style of genital touch, resulting in 12 commonly applied techniques that formed the basis for the episodes, each focusing on a different masturbation technique. In addition to providing the opportunity to practice the techniques, the feedback of the virtual women serves as an example for giving feedback to the partner during genital stimulation. The program also includes videos in which women describe their experiences with sexual pleasure and demonstrate the techniques used in masturbation. The efficacy of such serious gaming techniques and other innovations introduced by smartphone applications seem promising, and should be evaluated in an RCT setting.

A challenge for future trials is how to use continuous enhancement of an intervention during the course of the study in order to keep up with technological improvements. Rapid development and testing of a new technology can be achieved by constant refining of the product based on the repeated feedback of end-users, in close collaboration between researchers, designers, software developers and end-users. When the prototype has been sufficiently evaluated and improved, a larger RCT can be performed. Despite the lack of such an iterative process in our trial and the need for a revision, we would argue that our trial can be viewed as a “proof of principle” and provides a foundation for the future development of Internet-based psychosexual counseling programs for BC survivors and their partners.

Third wave CBTs
Another consideration in evaluating the content of the CBT program that we evaluated pertains to the emergence of ‘third wave’ CBTs, such as Mindfulness-based cognitive...
therapy and Acceptance and Commitment Therapy (ACT)\textsuperscript{42}. Our intervention was based primarily on the principles of second wave CBT, i.e., focusing on dysfunctional cognitions (e.g., thoughts, interpretations, attributions) and their influence on emotions and behavior. In this view, psychopathology is seen as a result of biased information processing, characterized by maladaptive beliefs and automatic thoughts, and therapy attempts to modify these cognitive processes\textsuperscript{42}. In contrast, third wave CBTs do not attempt to change or replace the cognitions, but rather aim to teach the patient to become aware of distressing cognitions, to realize that they are ‘just thoughts’ and not necessarily an accurate representation of reality, and to prevent an automatic response of rumination\textsuperscript{42}. There is thus a focus on the realization that the metacognitive processes are inaccurate - and therefore not the cognitions, but rather the metacognition or attitude towards these cognitions need to be changed\textsuperscript{43}. In sex therapy, mindfulness-based exercises can increase the awareness of pleasurable sensations\textsuperscript{44}, increase genital-subjective sexual arousal concordance\textsuperscript{45} and help patients to become less judgmental about the quality of the sensations or to not perceive them as below standard; an attitude-shift that might be particularly suitable for formerly sexually healthy BC patients who have to cope with an altered sexuality.

The effectiveness of Mindfulness-based (cognitive) therapy for female sexual dysfunctions has been demonstrated in the general population\textsuperscript{46-48} and in gynaecological cancer survivors\textsuperscript{49,50}. The effectiveness of ACT in the treatment of depression and anxiety has been established\textsuperscript{51-55}, but research into its effectiveness for sexual dysfunctions is still limited. First studies are being conducted, including a study evaluating the use of the theoretical framework of ACT to improve adherence to treatment for erectile dysfunction in prostate cancer survivors\textsuperscript{56}. In BC survivors, studies evaluating ACT and Mindfulness-based therapy for sexual problems are limited, but results from other trials seem promising and encourage the inclusion of third-wave CBT in future sex therapies for the BC population.

\textbf{Face-to-face and self-management interventions}

For reasons described in \textit{Chapter 4}, we compared our intervention group to a waiting-list control group only, and not to a group receiving face-to-face therapy. Research has shown that Internet-based CBT is as effective as face-to-face therapy for a range of psychological problems\textsuperscript{57}. We expected that this would also be the case for online sex therapy, especially considering aspects of online therapy such as anonymity and accessibility, which may be particularly attractive in the treatment of sexual problems. Nevertheless, a comparison of Internet-based and face-to-face sex therapy for BC survivors with a DSM-IV sexual dysfunction, preferably including a cost-effectiveness analysis, could be useful.

It might also be valuable to develop and evaluate an Internet-based sex therapy program that is suitable for BC survivors experiencing less severe sexual problems. The intervention described in this thesis involved an intensive therapy program. Such a program may be appropriate for the treatment of DSM-based sexual dysfunctions, but less so for milder
sexual problems. The prevalence rates of sexual problems in BC survivors are between 45% and 77%. However, only a small percentage of these women meets criteria for a DSM-diagnosis of sexual dysfunction and is in need of intensive therapy such as the one evaluated in our study. A ‘light’ version of our Internet-based therapy could be suitable for a larger group of women, and has the potential to be cost-effective. We therefore intend to develop and test, in an RCT context, a (guided) self-management version of our Internet-based CBT program targeting BC survivors experiencing milder sexual problems.

To date, the majority of self-management interventions have been developed for depression and anxiety and the available evidence indicates that they represent an effective treatment strategy. First studies have demonstrated the feasibility of self-management interventions in improving the sexual functioning of cancer survivors. In an unguided self-management program, participants complete a treatment protocol independently, without support of a therapist. Such a program consists primarily of psycho-educational information and instructions for exercises; minimal interventions that are effective in the management of sexual changes after cancer. In guided self-management, a counselor is available, typically via email or telephone, to provide support in working through the treatment program. Although research has indicated that guided self-management programs tend to be more effective than unguided programs, we intend to test both in a future RCT, including a cost-effectiveness evaluation.

Potential contamination
Although only the women in the intervention group of our trial received the therapist-guided Internet-based CBT program, being invited to participate in a large RCT focusing on sexual functioning after treatment of BC and having an intake interview with a psychologist/sexologist may have influenced the sexual functioning of women in the control group. The ‘permission for the sexual problems to exist’ provided by the study invitation and intake interview, and the limited information that was given in the patient information brochure and the booklet ‘80 vragen over kanker en seksualiteit’, may have encouraged women in the control group to search for solutions for their sexual problems and/or to discuss their sexual changes with their partner. This may explain the slight improvement in sexual functioning and decrease of sexual distress from baseline to post-CBT in the control group. These ‘minimal interventions’ can be viewed as the first two steps of the PLISSIT model (i.e., Permission, Limited Information, Specific Suggestions, Intensive Therapy). The idea that these minimal interventions may have slightly improved the sexual functioning of the control group is consistent with previous research demonstrating that providing psycho-education can improve the sexual functioning of gynaecological patients and cancer patients’ awareness of sexuality, communication with the partner about sex, and management of sexual changes. This idea further supports the need for the development of a ‘light’ version of our Internet-based CBT program.
Assessment of sexual functioning

A challenge in clinical trials evaluating the level of sexual functioning is how to handle sexual inactivity when assessing the level of sexual functioning. Several items of both the FSFI and IIEF include a response option ‘did not attempt intercourse’, which is assigned a score of zero. This shifts the scores towards the sexually dysfunctional end of the scale. This approach is used by most patient-reported outcome measures assessing sexual functioning. In response to this problem, some researchers choose, when evaluating the efficacy of sex therapy, to exclude all participants from their analyses who indicate that they are not sexually active. This approach may, however, affect the generalizability of the results, as it leads to a selection of the better functioning participants. We therefore chose to include sexually inactive couples in our analyses of the efficacy of our CBT program. Moreover, as we only included women with a DSM-IV sexual dysfunction, it seems likely that couple’s sexual inactivity was a reflection of this DSM-diagnosis and thus of low levels of sexual functioning.

Another disadvantage of the IIEF is that many of the items focus on sexual intercourse, i.e., penile penetration of the vagina. This reflects the traditional view of heterosexual sex as being synonymous with coitus; also known as the ‘coital imperative’. The coital imperative conveys the message that non-coital sexual activities are either meant to precede coitus, to be optional, or to be a substitute when coitus is not possible for some reason. The IIEF also includes an item querying about the frequency of coitus, with higher scores reflecting higher frequency. This assumes that more frequent intercourse reflects higher intercourse satisfaction and better overall sexual functioning. We would argue that using frequency of sexual activity as an indication of the quality of sexual functioning is a flawed approach. There are data that indicate that more frequent sex is not necessarily reflective of, and certainly not synonymous with, increased relationship satisfaction and satisfaction with life or happiness. Rather, aspects such as sexual desire, arousal and pleasure are considered to be better indicators of the quality of sexual functioning. Similar issues are present with the FSFI, as many items assess the degree of lubrication and ease of vaginal penetration. We would recommend that future questionnaires assessing sexual functioning should broaden their focus to include masturbation, oral and manual stimulation and sexual pleasure. Additionally, in questionnaires assessing female sexual functioning, clitoral stimulation should receive more attention, as only 25% of women experience orgasm through vaginal penetration alone.

Not only do these features of the questionnaires raise questions about their content validity, they may also affect the conclusions of clinical trials of sex therapy. As indicated in Chapter 7, the differential effects of the Internet-based CBT on the sexual functioning of BC survivors and their partners observed in our study (Chapter 4, 5 and 7) may, in part, be explained by the focus of the IIEF on coital activity. This may have limited our ability to detect sustained positive effects of the CBT program on male sexual functioning;
something that was less of an issue in assessing the impact of the program on the BC survivors, as the FSFI places more emphasis on sexual activity, in general.

**Assessments and follow-up**

In our trial, we did not ask women in the control group to complete the 3- and 9-month follow-up assessments. Thus we were unable to compare the long-term changes in the intervention group with those of the (untreated) control group. We also did not assess the sexual functioning, relationship intimacy and marital functioning of the partners of women in the control group, resulting in an observational study of only the partners of the BC survivors who had been exposed to the CBT program. We believe that these limitations were inevitable, given both our and the institutional review board’s position that it would be ethically inappropriate to withhold offering BC survivors who had initially been assigned to the waiting list control group the opportunity to follow the CBT program until the longer term follow-up had been completed. Similarly it was not considered appropriate to ask the partners of those randomly assigned to the control group to complete an extensive battery of questionnaires, given that they were neither invited to nor did they participate in the trial. Despite these design limitations, we believe that the long-term follow-up data on the intervention group and on their partners provide useful insights that complement the core of the clinical trial.

**Drop-out and predictors of therapy success**

Sixty-two percent of the intervention group completed the Internet-based CBT as planned (Chapter 4). This percentage is similar to completion rates observed in other trials of Internet-based interventions for psychological disorders, with an average drop-out rate of 31%\(^7\). We did not collect extensive data on the degree of adherence (e.g., number of completed interventions, log-in time, number of emails). Such data could have provided more insight into the factors that were predictive of therapy adherence. However, the optimal approach for measuring adherence in Internet-based therapies has not yet been established and further research is needed to understand the role of adherence on treatment outcomes\(^3\).

In our trial, we were also unable to investigate which specific elements of the online CBT program were more or less effective (Chapter 6). The CBT program was evaluated as a “package deal”. Future trials of eHealth interventions for sexual problems are needed to identify those features of the interventions that contribute most to therapy success, and those that are less salient.

The majority of the variables that we included as potential predictors of therapy success were similar to those used in the evaluation of face-to-face sex therapy, and our outcomes were consistent with the predictors of therapy success found in face-to-face treatments in the general population\(^74\) (Chapter 6). Research into the predictors of therapy response
and adherence to eHealth interventions seems promising, as log-data of eHealth programs can offer objective insight into the mechanisms that contribute to the effect of the intervention. So far, research has mainly focused on log-data such as number of completed modules, time spent and number of log-ins. Although this information is valuable, it assumes a dose-response relationship, and it does not reflect if the program fits well with the needs of the user or how the program is used (e.g., spending more time online does not necessarily reflect optimal or efficient use of the program). Future trials should evaluate how the use of different components of the treatment program or technology, or combinations of components, contribute to the efficacy of the treatment program.

Cost-effectiveness

The type of extensive sex therapy evaluated in our trial is not currently reimbursed by Dutch health insurance. As of 2014, psychosexual counseling is only reimbursed for patients with a DSM-diagnosis of paraphilia, gender identity disorder, hypersexuality, sexual dysfunction caused by another psychological disorder (e.g., depressive disorder), or if the psychosexual counseling is offered in the context of a hospital-based medical DBC (Dutch: Diagnose Behandel Combinatie) for treatment by a gynaecologist or urologist. The financial support of The Netherlands Cancer Institute enabled us to finance the costs of the therapy, so that we could successfully complete the trial. However, consequently, further implementation of the intervention in its current form is not financially feasible.

In 2017, our study was selected for a project of the Dutch Cancer Society in which the costs and benefits of several interventions targeting the quality of life of cancer patients was evaluated in the context of a Social Business Case. The Social Business Case is a structured cost-benefit assessment used to evaluate the economic and social usefulness of an intervention. The financial profit for society is evaluated by comparing the costs of the intervention with the potential social benefits. These benefits are estimated and quantified based on research, literature, assumptions, and advice of an expert group. With regard to cost savings for health insurers, it was estimated that our Internet-based CBT program would reduce patient visits to the general practitioner, the mental health counselor working in general practice offices (Dutch: Praktijkondersteuner Huisarts - Geestelijke Gezondheidszorg (POH-GGZ)) and the gynecologist. For patients, the Internet-based therapy resulted in a reduction in travel expenses and parking costs. A comparison of the total costs of the intervention with the total expected cost savings resulted in an expected financial profit of €0.14 per invested euro, and thus an expected loss of €0.86. It is important to note that this type of budget impact analysis expresses the benefits of an intervention in monetary terms, and does not take into account improvements in the patients’ quality of life. We would argue that this approach is less applicable to psychosocial interventions, as the benefits of these interventions are less well expressed in financial terms. It is also questionable as to whether it is reasonable to expect that such psychosocial interventions
should be expected to yield monetary profit for the larger community. Nevertheless, we recognize that the cost of our Internet-based CBT intervention, with sustained guidance by sex therapists via email, was high – €2,000 per patient. To be viable economically, less expensive models of Internet-based sex therapy need to be developed and tested.

**IMPLICATIONS FOR FUTURE RESEARCH**

To date, many studies have evaluated and demonstrated the effectiveness of CBT for a range of psychological problems, but less is known about the working mechanisms of CBT, i.e., which components are essential for a treatment program to be effective. A challenge in answering this question is the fact that CBT is a technically eclectic treatment including many components that might effectuate change\(^{85}\). Although an evaluation of the effect of different treatment components provides insight into which features of a therapy are effective, it leaves the question of how these changes occur unanswered\(^{86}\). The expansion of the range of CBTs with ‘third wave’ therapies, each with its own content and mechanisms of change, present additional challenges for researchers. Additionally, further research into the predictors and moderators of the success of (eHealth) interventions is warranted, to be able to select patients who will benefit most from the intervention or to tailor the content of an intervention to the needs of the individual patient.

To our knowledge, our study is the first to collect data directly from the partner him/herself during the course of CBT targeting the sexual dysfunction of one member of the couple. More research is needed to determine the optimal involvement of the partner in sex therapy after cancer treatment and the prerequisites to effectuate a sustained effect in the partner’s sexual functioning.

Lastly, given the very rapid advances in the development of eHealth interventions and related technology, future trials are needed that enable continuous enhancement of the intervention during the course of the study\(^{41}\). Constructive Technology Assessment (CTA) can be used to investigate this dynamic process, as it enables a continuous evaluation of relevant clinical, economic, patient-related and organizational aspects in the development of a new technology\(^{87}\). CTA attempts to influence technological design and implementation with the aim of improving the effectiveness of the technology in clinical practice, and uses traditional social sciences techniques, such as process analysis, scenario analysis and various forms of cost(-effectiveness) analyses\(^{87}\). These analyses evaluate and anticipate potential barriers that may be encountered in clinical adoption and therefore facilitate the uptake of dynamic types of interventions, such as Internet-based therapies.
CONCLUSIONS

The sexual functioning of BC survivors as well as that of their partners is affected by the disease and its treatment. Our Internet-based CBT program realized long-term improvement in the sexual functioning, sexual distress and body image of BC survivors. Although partners did not report sustained positive effects of the intervention on sexual functioning, they did benefit in terms of overall sexual satisfaction, feelings of sexual intimacy and sexual relationship satisfaction. The involvement of the partner in treatment improved the women’s therapy compliance, which subsequently increased the women’s post-CBT sexual functioning and decreased post-CBT sexual distress. The combination of these latter two findings advocates for the involvement of both partners in therapy. Future Internet-based interventions should involve the partner to a greater extent, by building in to such programs modules specifically targeting male sexual dysfunction.

To ensure that the intervention is available to patients, it is important that health care professionals discuss the potential impact of treatment on sexuality with BC survivors, and that they query women and their partners about sexual functioning during follow-up. This will enable the health care professionals to select the patients in need of professional help, and will give BC patients “permission” to discuss their sexual problems.

More information is needed on the cost-effectiveness of Internet-based sex therapy programs for sexual dysfunction after BC. Since methods such as a Social Business Case evaluate the treatment effects in financial terms only, this type of cost-benefit analysis is less suitable for the evaluation of psychosocial interventions, which primarily effectuate change in quality of life. As such, a cost-effectiveness analysis, which also focuses on gains in terms of quality of life, for instance by evaluating the Quality Adjusted Life Years (QALYs), may be more appropriate for Internet-based sex therapy.

A potentially cost-effective alternative to the intervention evaluated in this thesis could be a self-management version of the CBT program. Another benefit of such a ‘light’ version of our program is that it could be offered to the many BC survivors who experience milder sexual problems after BC treatment. The intervention described in this thesis can be viewed as a proof of principle for the efficacy of Internet-based CBT for sexual dysfunctions in BC survivors.
REFERENCES


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