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PH.D. THESIS SUMMARY

ATTENTIONAL BIASES AND RESPONSE EXPECTANCIES IN BREAST CANCER PATIENTS UNDERGOING CHEMOTHERAPY

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Notes: _____

(1) This is to certify by Oana Cobeanu that:

1. The thesis includes the original research work of Oana Cobeanu (author) towards the Ph.D.;
2. Parts of this thesis have been accepted for publication or presented as conference papers; appropiate citations for these publications were included in the thesis. Other co-authors have been included in the publications if they contributed to the exposition of the published text, data interpretation, etc. (their specific contribution was clearly explained in the footnotes of the thesis);
3. The thesis was written according to the academic writing standards. All the text of the thesis and its summary was written by Oana Cobeanu who assumes all responsability for the academic writing; also:
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(2) This is to certify that Ms. Cobeanu attended the courses on Principles of Ethics at the Doctoral School "Evidence Based Psychological Assessment and Interventions"

(3) All the Tables and Figures are numbered within the corresponding chapter or subchapter of the thesis.

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Key words: cognitive-behavioral psychotherapy, attentional biases, response expectancies, attentional bias modification (ABM) paradigm, distress, side effects, chemotherapy, breast cancer

CHAPTER I. THEORETICAL BACKGROUND

Breast cancer is the most common type of cancer in women worldwide, comprising 16% of all female cancers. About 519 000 women died in 2004 due to breast cancer, and 1.38 million new breast cancer cases were diagnosed in 2008 around the world (World Health Organization, 2008). Most patients with breast cancer, following or prior to surgery, will require other medical treatments (e.g., radiotherapy, chemotherapy, hormone therapy or a combination of these) delivered in order to either sustain primary treatment (i.e., neo-adjuvant therapy) or increase the chances of long-term survival post-primary treatment (i.e., adjuvant therapy). These treatments are usually accompanied by physical side effects (e.g., nausea, vomiting, hair loss, fatigue, pain), but also emotional distress. Due to the increasing medical advances, breast cancer treatments today are likely to have less dramatic consequences on one's physical aspect from surgery than years ago, but are more complex and extend over a longer period of time ("Psychological and Social Aspects of Breast Cancer - Cancer Network," 2008). Similar with the majority of cancers, relative survival for breast cancer is improving and, consequently this disease may be conceptualized as a chronic one (White, 2001).

The majority of breast cancer patients will experience a period of psychological distress and some of them will develop psychological disorders. According to the National Institute for Health and Clinical Excellence (NICE) (2009) between 22 and 47% of breast cancer patients may have an episode of significant anxiety and depression. Burges et al.(2005) have assessed the prevalence of clinically significant anxiety and depression in the five years following diagnosis of breast cancer. They found that point prevalence of depression, anxiety, or both (including borderline cases) was 33% at diagnosis and 24% at three months after diagnosis, dropping to 15% at one year. The authors conclude that in women with early breast cancer, prevalence of depression, anxiety or both is around twice that of the general female population, in the year following diagnosis. After this time point, women show similar levels of depression and anxiety to the general female population.

Moreover, there is evidence that in relation to general distress, the impact of treatment must be taken into consideration. Jim et al. (2007) have shown that greater physical symptoms/side effects experienced during adjuvant treatment (i.e., chemotherapy, radiotherapy or both) predicted greater total cancer-related distress, intrusive thoughts, and general distress, post-treatment. Follow-up analyses indicated that the relationship between physical symptoms/side effects and general distress was mediated by both total cancer-related distress and intrusive thoughts. These results suggest that patients who experience greater physical symptoms/side effects during treatment are at greater risk for later cancer-related distress and, in turn, general distress. Taking this into consideration, it seems indicated to investigate the efficacy of psychological interventions delivered in the context of active breast cancer treatment and oriented towards helping women cope better in this context, both emotionally and physically.

This bidirectional relationship between distress and the experience of side effects, during a course of breast cancer treatment, can be explained, in the cognitive-behavioral framework (Beck, 1976; Ellis, 1994), by common cognitive mechanisms (i.e., dysfunctional beliefs).

CBT has shown promising results in cancer patients (Ferlay et al., 2010; Luebbert, Dahme, & Hasenbring, 2001), regarding distress experienced by these patients, their quality

of life or adjuvant treatment side effects like nausea and vomiting (Richardson et al., 2007). However, findings regarding the efficacy of CBT interventions on managing cancer adjuvant treatment related side effects and specifically in breast cancer patients undergoing treatment are scarce and inconclusive. We believe it is highly important to ascertain whether CBT is effective and adequate in the specific circumstances of the acute treatment setting, considering the significant amount of physical and psychological distress associated with this context (Burgess et al., 2005; Jim et al., 2007; David Spiegel, 1997).

In order to fulfill this aim, we have oriented our attention towards the role played by *response expectancies* and *attentional biases towards side effects of treatment*. Consequent to recent developments of the Attention Bias Modification (ABM) interventions field, showing significant effects on distress outcomes (Hakamata et al., 2010; Hallion & Ruscio, 2011), as well as promising results on somatic ones (Sharpe et al., 2012), and taking into consideration the significant percentage of women experiencing anxiety and depression after receiving a diagnostic of breast cancer (Burgess et al., 2005), we considered expanding attentional bias and ABM interventions research on the breast cancer clinical population. In this attempt, we also decided to integrate the important body of research on response expectancies and CBT interventions that target response expectancies, in breast cancer patients. We already know that response expectancies play a central role in the generation of non-volitional outcomes like side effects of treatment and associated distress (Montgomery & Bovbjerg, 2000; Montgomery et al., 2010; Sohl et al., 2009). For this last aim, a CBT framework represented the main guideline.

Second, as research on attentional biases has developed somehow independent of the CBT framework, we aimed to establish possible mediating/moderating relationships between central CBT constructs like irrational beliefs/dysfunctional attitudes and/or automatic thoughts and attentional bias. Similarly, we explored possible mediating/moderating relationships between response expectancies (i.e. as automatic inferential beliefs) and attentional bias, in relation to their effect on distress and side effects of treatment.

Third, given the obvious advantages of ABM interventions of being cost-effective and easily to disseminate (as they rely on simple, repetitive cognitive exercises that can be learned easily and practiced independently, with minimal assistance from a mental health professional), new possibilities for psychological interventions delivered in the context of ambulatory cancer treatment arise. In this sense, drawing on recent research on CBT plus ABM interventions used in the management of pain (Sharpe et al., 2010, 2012), we have developed an enhanced CBT protocol, through the adding of an ABM intervention designed to retrain attention away from stimuli describing side effects of treatment.

The relevance of our research stands mainly in the integration of response expectancies and attentional bias research, under the CBT framework, in the breast cancer clinical population. Further on, this integration represents the necessary ground for building CBT enhanced interventions that target both attentional biases, as well as response expectancies.

In the next chapter we outlined the research objectives and the overall methodological approach employed to reach these objectives, in order to create the general framework for the understanding of the studies included in this research project.

CHAPTER II. RESEARCH AIMS AND OVERALL METHODOLOGY

Taking into account the theoretical and empirical considerations outlined in the previous chapter, we describe below the objectives of this thesis, together with the proposed research plan to achieve these goals.

The general goal of this research project was to investigate from a CBT perspective the role that response expectancies and attentional bias play together in the generation of emotional and physical distress experienced by breast cancer patients undergoing chemotherapy. More specifically, we wish to investigate a new treatment approach (i.e., attentional bias modification; ABM) for breast cancer patients undergoing treatment, in terms of its efficacy and mechanisms of change.

The first major objective of our research was to quantitatively review the data available in the literature regarding the clinical efficacy of CBT designed to reduce distress and side effects of neo-adjuvant or adjuvant treatment, in breast cancer patients. We decided to orient our research efforts in this direction as 1) no other previous systematic review looked at this specific matter; 2) we needed to establish a state of the art regarding CBT interventions for this specific category of patients (i.e., breast cancer patients undergoing neo-adjuvant or adjuvant treatment). This objective aimed to contribute to the empirical evidence regarding the CBT interventions' clinical efficacy and was pursued by means of a quantitative meta-analysis (Study 1).

The second major objective of our research was to pilot the use of attentional bias assessment and modification procedures, on a similar sample to the breast cancer patients. We selected menopause women, experiencing problematic physical symptoms, secondary to the menopause. As research on menopause symptoms has benefited from a cognitive behavioral conceptualization, we were able to easily integrate our research on response expectancies and attentional bias with the current findings in this domain. This objective was pursued by means of a single group, pre-post design.

The third major objective of our research was to extend previously reported results regarding attentional bias in breast cancer patients, as well as response expectancies for side effects. The objective had conceptual and methodological implications. In order to accomplish this objective we ran an exploratory correlational predictive study. We investigated the role of attentional bias as a potential predictor of response expectancies, distress and side effects of treatment. Conversely, we investigated the role of response expectancies in predicting attentional bias, distress and side effects of treatment (Study 3).

Finally, our **fourth major objective** was to integrate an ABM intervention in a classical CBT protocol designed for the management of side effects of treatment in breast cancer patients. More specifically we compared an ABM enhanced CBT protocol with the standard CBT protocol alone (i.e., relaxation plus guided imagery and specific suggestions for reduced chemotherapy side-effects), analyzing separately the effects of these two interventions on (1) side effects of chemotherapy and distress, as well as their effect on (2) response expectancies and attentional bias. In order to accomplish this objective we ran a randomized clinical trial.

Our studies (with the exception of Study 1) are fundamental research studies, aimed to advance the current understanding of the relationship between attentional bias and

response expectancies in generating emotional and physical distress in breast cancer patients undergoing treatment. All four studies have important clinical implications, as they offer guidelines regarding psychological treatment of choice for breast cancer patients undergoing treatment (Study 1 and Study 4), while also advancing current understanding on the importance of response expectancies and attentional bias for the clinical management of problematic menopause symptoms (Study 2) and side effects of treatment in breast cancer patients (Study 3).

A general outline of the Ph.D. research project is presented in Figure 1.

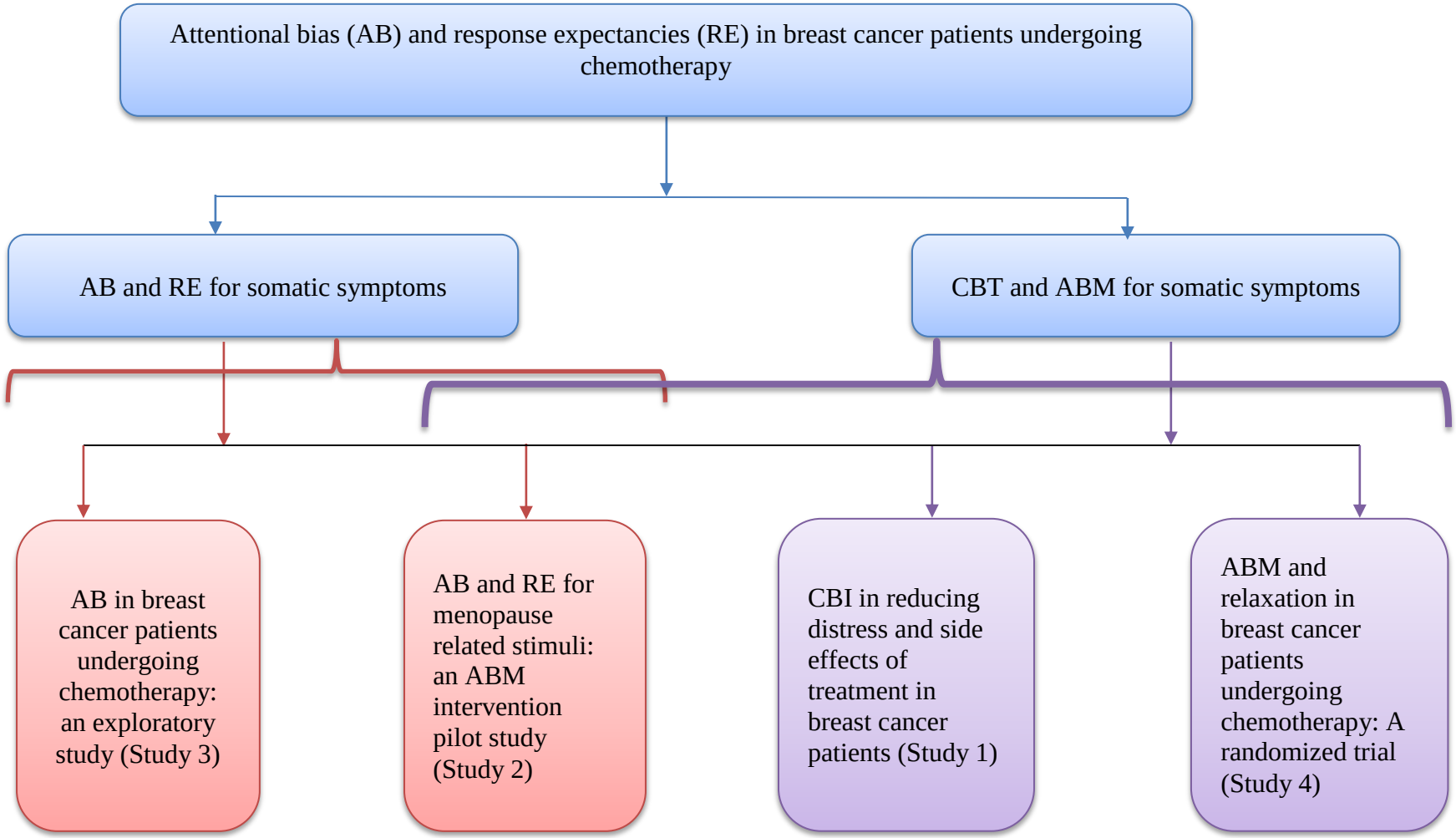

Figure 1. The schematic structure of PhD studies

CHAPTER III. ORIGINAL RESEARCH

STUDY 1: Can cognitive behavioral interventions alleviate the experience of side effects and distress in breast cancer patients undergoing treatment. A systematic review[1]

Introduction

Cognitive behavioral therapy (CBT) has shown promising results in cancer patients, regarding global affect, depression and quality of life (Graves, 2003), whereas specific behavioral interventions (e.g., relaxation, hypnosis) seem to significantly improve cancer treatment side effects like nausea, vomiting and pain (Luebbert, Dahme, & Hasenbring, 2001; Richardson et al., 2007), as well as depression and anxiety (Luebbert et al., 2001). Two previous quantitative meta-analyses on the efficacy of CBT and CBT techniques for breast cancer patients have been reported (Naaman, Radwan, Fergusson, & Johnson, 2009; Tatrow & Montgomery, 2006).

In their analysis, Tatrow and Montgomery (2006) considered distress and pain as main outcomes. When adjusting for sample size (see Hunter & Schmidt, 1990) the effect sizes reported for both distress and pain were not significantly different from zero. The authors reported (1) a larger effect size for the individual therapy format as compared to the group format, (2) no correlation between the number of psychotherapy sessions and effect sizes, and (3) no differences related to cancer severity (metastases vs. no metastases). However, these moderation analyses were conducted using unadjusted mean effects sizes.

Naaman et al. (2009) reported on the efficacy of CBT, guided imagery and relaxation techniques, and also supportive – expressive interventions and educational interventions. They focused on anxiety, depression and quality of life outcomes and included studies run on samples of patients with different breast cancer stages, having undergone surgery, being currently under or following an adjuvant treatment. Their results showed that CBT had a non-significant effect on anxiety and a large effect on depression. Similarly, guided imagery and relaxation (only one study) (Bridge, Benson, Pietroni, & Priest, 1988) had a small effect on anxiety and a medium effect on depression. Regarding quality of life outcomes, the authors reported a large effect size of CBT. However, only three studies were included in this analysis.

A number of shortcomings of previous meta-analyses on this topic emerge. Heterogeneity of studies included, in terms of 1) intervention protocol and 2) patients' stage of disease and stage of treatment, might have led to some non-significant findings regarding the efficacy of cognitive and/or behavioral interventions (CBI). Therefore, we believe that by specifically selecting CBI protocols (i.e. cognitive-behavioral protocols, cognitive protocols or behavioral protocols) a more accurate image on their efficacy in breast cancer patients will

[1] This study is under review at *Journal of Clinical Psychology in Medical Settings* (Impact Factor 1.366): Cobeanu, O. & David, D., (2013). Alleviation of Side Effects in Breast Cancer Patients by Cognitive Behavioral Interventions: A Systematic Review and Meta-Analysis.
The authors contributed to the manuscript as follows: Cobeanu, O. – study design, study implementation (including data analysis), writing the manuscript; David, D. – study design, structuring the manuscript, consultation for writing the manuscript.

be provided. This approach is of real importance in the light of the already proven efficacy of cognitive-behavioral treatments in treating depression and anxiety disorders (Butler et al., 2006), chronic pain (Morley, Eccleston, & Williams, 1999), as well as distress in cancer patients (Graves, 2003; Luebbert et al., 2001).

We believe it is highly important to ascertain whether CBI are effective and adequate in the specific circumstances of the acute treatment setting (see also (Luebbert et al., 2001), considering the significant amount of physical and psychological distress associated with this context. At this point, reports regarding the efficacy of CBI in managing breast cancer treatment side effects are scarce and inconclusive. Previous quantitative reviews have not specifically addressed the effect of CBI on treatment side effects in breast cancer patients. Only qualitative reports consider side effects like nausea and vomiting or fatigue as main outcomes of interest. Hence, there is still need for information on how CBI influences the severity and/or frequency of these specific symptoms in breast cancer patients.

This meta-analysis aimed to 1) investigate the efficacy of CBI in breast cancer patients with regard to distress and quality of life, using more restrictive inclusion criteria; 2) extend the previous reported narrative results with respect to CBI effect on overall and specific side effects (i.e. fatigue, sleep disturbances, nausea and vomiting) of medical treatments. Specifically, we aimed to: 1) establish an average effect size estimate of CBI for breast cancer patients undergoing treatment; 2) provide average effect size estimates for treatment related side effects, emotional distress and quality of life; 3) test possible moderators of CBI effect.

A very important aspect of this meta-analysis is that decided to include only studies that reported interventions built within a cognitive and/or behavioral approach, as described by the authors, delivered during the course of breast cancer treatment and oriented towards alleviating side effects and/or emotional distress. We have focused on the specific circumstances of breast cancer patients receiving treatment as we wish to provide useful clinical information, in order to serve health professionals involved in the cancer treatment process.

Methods

Literature Search

Potential relevant studies were identified through a search of the PsychInfo and MEDLINE databases through April-December 2012, using the following search terms and combinations thereof: “breast cancer”, “chemotherapy”, “radiotherapy” “relaxation therapy”, “cognitive behavioral psychotherapy”, “cognitive behavioral intervention”, “CBT”, “hypnosis”, “pain”, “nausea”, “vomiting”, “fatigue”, “sleep disturbances”, “side effects”, “cognitive intervention”, “behavioral intervention”, “symptom management”.We also systematically searched the references from recent randomized clinical trials, meta-analyses and reviews on the topic.

Inclusion criteria

The following criteria were applied for inclusion in the meta-analysis: 1) the study was a randomized clinical trial; 2) the study was designed specifically to assesses the efficacy of a cognitive and/or behavioral intervention (CBI) in managing side effects of breast cancer treatment and/or associated distress; 4) the study was written in English; 5) sufficient data to

compute effect size were available. We did not include studies that: 1) investigated the efficacy of CBI in breast cancer patients before or after treatment or which were oriented towards alleviating surgical distress; 2) studies that investigated the efficacy of CBI in managing physical symptoms not associated with side effects of treatment (e.g., pain associated with metastasis).

Coding procedures

For every eligible study we retained the following variables: study identification data (i.e., author, year of publication), type of outcome reported (i.e. side effects of treatment - SE, distress – D, and quality of life - QoL), sample size, mean age of participants, clinical status of the sample (stage of breast cancer), subjects prior experience with the medical treatment, type of medical treatment, professional status of the person(s) delivering the psychological intervention, length (in hours) of the psychological intervention, description of the psychological intervention, therapeutic orientation (based on the authors description of the protocol), type of psychological intervention (individual or group therapy), outcome measures, and time points of collecting data.

Statistical analyses

For all sets of the calculated effect sizes we used the random effects model. Weighted effect sizes ≥ 2 *SD* above or below the weighted mean effect size were considered outliers. In order to address the publication bias, we calculated a fail-safe *N* for all effect size subsets (Rosenthal, 1991). In addition, we generated and visually examined a funnel plot, which plots standard error for each study (determined by sample size) against the effect size computed for that study. Next, we used Duval and Tweedie's (2000) trim-and-fill procedure to estimate the likely number of missing studies that would correct the publication bias. All the analyses were run using Comprehensive Meta-Analysis, Version 2.2.046 (Borenstein, Hedges, Higgins, & Rothstein, 2005).

CBI Overall Effect

The overall effect of CBI, including all outcomes, was calculated from data reported in 18 studies (including a total of 2037 participants), at post-intervention. The results showed a small, but statistically significant overall effect size, Cohen's $d = 0.32$, $p = 0.000$, 95% CI = [0.168; 0.478]. The overall results for follow-up measures (including data reported in 8 studies, with a total of 1294 participants) revealed a significant, small overall effect of CBI, $d = 0.35$, $p = 0.016$, 95% CI = [0.066, 0.646].

CBI Effect on Side Effects of Treatment

The effect of CBI on overall side effects of treatment (e.g. nausea and vomiting, fatigue, pain, sleep disturbances, muscle weakness, bowel pattern, breast symptoms, arm symptoms) was calculated from a number of 10 studies (including a total of 1140 participants), considering only data reported post-intervention. Results showed a small, but statistically significant overall effect size, Cohen's $d = 0.31$, $p = 0.005$, 95% CI = [0.093; 0.530]. There was evidence of heterogeneity, Q (9) = 26.786, $p = 0.002$, $I^2 = 66.400$.

Further on, we computed separated effect sizes of CBI on 1) nausea and vomiting, 2) fatigue, 3) sleep disturbances and 4) pain.

Nausea and vomiting

The effect of CBI on nausea and vomiting was calculated from a number of 5 studies (including a total of 518 participants), considering only data reported post-intervention. The results showed a small, but statistically significant effect size, Cohen's d = 0.39, p = 0.000, 95% CI = [0.217; 0.575].

Fatigue

The effect of CBI on fatigue was calculated from a number of 6 studies (including a total of 831 participants), considering only data reported post-intervention. The results show a non-significant effect size, Cohen's d = 0.34, p = 0.063, 95% CI = [-0.019; 0.710]. There was evidence of heterogeneity, Q (5) = 31.197, p = 0.000, I^2 = 83.973.

Sleep disturbances

The effect of CBI on sleep disturbances was calculated from a number of 3 studies (including a total of 387 participants), considering only data reported post-intervention. The results showed a small non-significant effect size of CBI, Cohen's d = 0.25, p = 0.314, 95% CI = [-0.244; 0.761].

Pain

The effect of CBI on pain was calculated from a number of 3 studies (including a total of 397 participants), considering only data reported post-intervention. The results showed a nonsignificant effect of CBI on pain, Cohen's d = - 0.02, p = 0.854, 95% CI = [-0.259; 0.214].

CBI Effect on Distress Outcomes

The effect of CBI on overall distress (e.g. measures of anxiety and depression, mood rating, perceived stress, negative and positive affect, psychological distress, overall distress, hostility; see also Table 1) was calculated from a number of 16 studies (including a total of 1831 participants), considering only data reported post-intervention. The results showed a small, but statistically significant overall effect size, Cohen's d = 0.30, p = 0.000, 95% CI = [0.134; 0.476].

Further on, we also computed separated effect sizes of CBI on anxiety and depression, respectively.

Anxiety

The effect of CBI on anxiety was calculated from a number of 8 studies (including a total of 1083 participants), considering only data reported post-intervention. The results showed a significant small effect of CBI, Cohen's d = 0.28, p = 0.033, 95% CI = [0.023; 0.538].

Depression

The effect of CBI on depression was calculated based on data reported in 10 studies (including a total of 1202 participants), at post-intervention. The results showed a small non-significant effect of CBI, Cohen's d = 0.21, p = 0.063, 95% CI = [-0.012; 0.448], with evidence of heterogeneity, Q (9) = 30.036, p = 0.000, I^2 = 70.036.

CBI Effect on Quality of Life

The effect of CBI on quality of life was calculated from a number of 8 studies (including a total of 1139 participants), considering data reported post-intervention. The results showed a small to medium significant effect of CBI, Cohen's d = 0.45, p = 0.000, 95% CI = [0.209; 0.691]. See Table 1 for a complete list of effect sizes for every outcome.

Table 1. *Effect sizes for every outcome, at post-treatment*

	Effect size (Cohen's *d*)	**No. of studies (*k*)**	**N**
Physical domain	.31**	10	1140
Nausea and vomiting	.39**	5	518
Pain	-.02	3	397
Fatigue	.34	6	831
Sleep disturbance	.25	3	387
Distress	.3**	16	1831
Anxiety	.28*	8	1083
Depression	.21	10	1202
Quality of life	.45**	8	1139

Notes. *p < 0.05, **p < 0.01; d < 0.2, no impact of intervention, d = 0.2 – 0.5, small impact of intervention, d = 0.5 – 0.8, medium impact of intervention, d > 0.8, large impact of intervention

Publication Bias

We computed a fail-safe *N* for the overall effect of CBI at post-treatment. The number of studies that would reduce the effect size to non-significance was 180. This number supports the robustness of the computed effect size, as Rosenthal (1991) claims that computed fail-safe *N* should be larger than 5*K*+10 (where *K* is the number of studies included in meta-analysis) in order to indicate a robust effect size. As we included 18 studies reporting data at post-treatment, the fail-safe *N* would be expected to be more than 100.

We also computed a fail-safe *N* for the effect of CBI on overall distress outcomes (N = 126 > 5K+10), anxiety (N = 29 < 5K+10), side effects of treatment outcomes (N = 49 < 5K+10) and quality of life outcomes (N = 86 > 5K+10). For anxiety and side effects of treatment outcomes, the computed fail-safe *N* did not support the robustness of the computed effect sizes. Only in the case of quality of life outcomes, Duval and Tweedie's (2000) trim-and-fill procedure suggested two missing studies, which would reduce the mean effect size to d = 0.31 , 95% CI = [0.033; 0.588].

Moderators of CBI Effect

We found no significant moderator for the effect of CBI on any of the outcomes. However, we identified a trend indicating a possible moderating role of type of therapy (i.e., individual vs. group therapy) on overall distress. Individual therapy showed a significant small to medium effect size on overall distress outcome (k = 7; d = 0.40, p = 0.000, 95% CI = [0.187; 0.626], $Q(6)$ = 14.146, p = 0.028, I^2 = 57.587), whereas group therapy showed a small non-significant effect size on the same outcome (k = 6; d = 0.15, p = 0.144, 95% CI = [-0.053; 0.363], $Q(5)$ = 9.156, p = 0.103, I^2 = 45.390).

Also, in relation to overall side effects of treatment, behavioral interventions showed a significant small effect size (k = 8; d = 0.31, p = 0.005, 95% CI = [0.098; 0.539], $Q(7)$ = 17.906, p = 0.012, I^2 = 60.907), whereas cognitive-behavioral interventions showed a small non-significant effect (k = 4; d = 0.36, p = 0.138, 95% CI = [-0.117; 0.842], $Q(3)$ = 8.880, p = 0.031, I^2 = 66.215).

Discussion

This meta-analysis revealed a small, but significant effect of CBI on side effects of treatment, overall distress and quality of life in breast cancer patients, at post-treatment and also at follow-up. These results indicate that 62% of patients in the control groups did worse than the average intervention group patient (McGough & Faraone, 2009). We found no evidence of publication bias for the overall effect of CBI.

When analyzing specific side effects outcomes, we found that CBI are efficient in reducing patients' nausea and vomiting, but not their fatigue, pain or sleep disturbances, during treatment. CBI had a small, but significant effect on anxiety. We did not find a significant effect of CBI in addressing depressive symptomatology reported by breast cancer patients.

We found no significant moderators for the effect of CBI on any of the outcomes considered in the moderation analysis. However, patients in the individual therapy format as opossed to the group format seem to respond better to therapy, in that their emotional distress significantly decreased. Also, patients receiving behavioral interventions as opossed to cognitive-behavioral ones seem to report less intense and/or frequent side effects of treatment. In the context of acute treatment, behavioral interventions (e.g., relaxation exercises, stimulus control) may be more likely to register a positive effect on side effects of treatment than cognitive-behavioral interventions.

The results of this meta-analysis are relevant for both patients and clinicians, in the specific context of acute treatment for breast cancer. Information provided by our study can be used in the development of interventions for breast cancer patients undergoing treatment. However, further research is necessary in identifying more efficient cognitive-behavioral protocols for specific side effects like pain, fatigue and sleep disturbances, during breast cancer treatment.

STUDY 2: Attentional bias towards-menopause related stimuli and its relationship with response expectancies and symptom reports: a pilot study of an ABM intervention[2]

Introduction

Hot flushes and night sweats (HF/NS) affect 65–85% of women after breast cancer treatment, often occurring while women are still adjusting to the effects of cancer treatments. HF/NS are more severe in this population than they are in healthy women and have a negative effect on quality of life, mood, and sleep (Carpenter, Johnson, Wagner, & Andrykowski, 2002; Hunter et al., 2004). However, approximately 20% of menopausal women report having problematic hot flushes and night sweats (HF/NS) which impact on sleep, mood and quality of life, with many of them preferring non-medical treatment options (Hunter, 2003).

Considering the cognitive-behavioral framework, context specific dysfunctional beliefs are influenced by the general cognitive style of an individual, meaning that general dysfunctional beliefs/attitudes would lead to different particularizations (i.e., negative response expectancies for menopausal symptoms, attentional bias towards menopausal symtoms), depending on the individual's relevant activating events.

We considered the menopausal women population, its health context and the cognitive-behavioral rationale offered for its symptoms as highly appropriate for piloting an attentional bias assessment and retraining tasks, prior to their implementation with breast cancer patients.

The aims of this study were 1) to investigate the presence of an attentional bias towards menopause symptom-related negative words in women with problematic menopausal symptoms; 2) to investigate the efficacy of an ABM intervention on reducing reports of menopausal symptoms. Finally, we developed this study as a pilot investigation, aiming at testing the feasibility of using computerized tasks, mainly the dot probe task, in a sample of women similar with the breast cancer patients group, in terms of problematic symptoms experienced and associated cognitive-behavioral rationale.

Methods

Design and statistical methodology

This study is a single group, pre-post design assessing the impact of an attentional bias modification intervention (ABM) on hot flush problem rating in women with problematic hot flushes and night sweats (HF/NS) during the menopause transition.

[2] Parts of this study were presented at the British Association for Behavioural and Cognitive Psychotherapies (BABCP) Conference 2013: Stefanopoulou, E., Cobeanu, O. & Hunter, M. (2013). "The impact of an attentional bias modification (ABM) intervention on reducing attentional bias and symptom reporting in women experiencing troublesome menopausal symptoms: An exploratory study"(poster presentation)

Participants

Fifteen women with menopausal symptoms were recruited from the local community (i.e., data were collected at King's College, Guy's Hospital Campus, London, UK; see the Procedure section for details) using posters placed in community settings and relevant websites. Inclusion criteria were at least 10 hot flushes per week for at least a month, assessed by the Hot Flush Rating Scale (Hunter & Liao, 1995).

Measures

Primary outcomes measures.

The Hot Flush Rating Scale (Hunter & Liao, 1995) provides a measure of hot flush frequency and a measure of the extent to which the hot flushes are problematic

The 7-items Generalized Anxiety Disorder Questionnaire (GAD-7; Spitzer, Kroenke, Williams, & Löwe, 2006) screens for and measures severity of generalised anxiety disorder.

Mechanisms of change measures (self-report).

The Dysfunctional Attitudes Scale – Short Form (DAS-SF; de Graaf, Roelofs, & Huibers, 2009) measures intensity of dysfunctional attitudes, as a feature of depression.

Visual Analogue Scales (VAS's) were used to measure response expectancies for problematic menopausal symptoms. This approach has shown good reliability in multiple studies (e.g., Montgomery & Bovbjerg, 2004; Montgomery & Kirsch, 1997).

ABM task – assessment of attentional bias and attentional retraining

Participants were presented with a number of word pairs stimuli (symptom-related and neutral words, e.g. flush-hat) on the computer screen and were asked to follow a probe of either the letter "p" or "q'" that repeatedly replaced them. We used menopause related word stimuli derived from qualitative studies on women's representation and experience of menopause (e.g. flush, redness) (Hunter et al., 2009). For the neutral word stimuli we used the Affective Norms for English Words (ANEW)(Bradley & Lang, 2010), which provides a set of normative emotional ratings for a large number of words in the English language.
Before every word pair, participants were presented with a fixation point (cross) for 500 ms in the center of the computer screen.

The task was completed during all 4 weekly sessions and consisted of 3 parts: an initial assessment phase (64 trials); ABM intervention stage (80 trials) and a post-ABM assessment phase (64 trials). During the two assessment stages, the probe appeared randomly in the location as one of the words ("p" or "q'" over either neutral or stimuli related words). During ABM intervention stage, the probe ("p" or "q'") appeared in the location of the target neutral word only. Hence the training implicitly directed participants to attend away from symptoms-related words. During all assessment and ABM stages, participants were asked to indicate as quickly as possible whether a 'p' or a 'q' appeared by pressing the corresponding key on a computer keyboard. The probe disappeared when a response was recorded. The next trial started after a delay of 500 ms. During this task, the program recorded the reaction time and accuracy of the responses (i.e. number of correct responses) for each of the trials (for all assessment and ABM stages).

Procedure

The study was developed in collaboration with the Department of Psychology, at King's College, in London, UK. The data were collected at King's College, Guy's Hospital Campus, by affiliated researchers. Women who expressed interest in the study (by telephone or e-mail) were asked a few questions over the telephone to determine eligibility. Those who met the inclusion criteria were sent an information sheet, consent form and assessment questionnaires, which they were asked to bring completed to the first session. Participants attended four sessions of attentional bias modification (ABM) at Guy's Campus. At the end of the final session of ABM, women completed a further set of questionnaire measures (the same as at baseline).

All women were seen by a researcher during the ABM intervention (4 weeks). Each weekly visit did not last for more than 30-45 minutes. The duration of the study for each participant was approximately 1 month.

Results

Table 1. Descriptive Statistics (baseline)

Variable	N	Minimum	Maximum	Mean	Std. Deviation
AB	15	-35.37	31.01	.93	18.57
DAS	13	17.00	93.00	46.61	17.97
GADQ	14	.00	18.00	4.21	4.72
No. HF/NS	14	28.00	126.00	53.85	26.04
PBLRT	15	3.00	10.00	6.60	1.99
VAS RE	15	1.30	9.97	6.03	2.45

Note: AB = Attentional Bias; DAS = Dysfunctional Attitude and Belief Scale; GADQ = Generalized Anxiety Disorder Questionnaire; No. HF/NS = Number of hot flushes and night sweats; PBLRT = Problem rating of hot flushes and night sweats; VAS = Visual Analogue Scale; RE = Response Expectancies

Nine of the participants showed positive bias scores, thus an attentional bias towards words describing menopause symptoms, while the remaining 6 showed negative bias score, thus attentional avoidance from threat. We did not find any significant correlations between the variable investigated, as was expected due to the small sample size.

Mean score for attentional bias at baseline was not significantly different from zero (One Sample *t* test, t (15) = .195, p = 0.848). Paired sample *t* test showed no significant difference between attentional bias, dysfunctional attitudes, symptoms of anxiety and response expectancies considered pre to post-ABM intervention ($p > 0.05$). However, mean scores for symptoms problem rating were significantly reduced post-ABM (t (12) = 2.213, p

= .047). Similarly, number of hot flushes/night sweats showed a trend toward significant reduction post-ABM (t (11) = 1.860, p = .090).

Discussion

The aims of this study were 1) to investigate the presence of an attentional bias towards menopause symptom-related negative words in women with problematic menopausal symptoms, and 2) to investigate the efficacy of an ABM intervention on reducing reports of menopausal symptoms.

First, we were unable to identify an attentional bias toward menopause symptoms. However, the small sample size might have influenced this result. Second, preliminary findings from this study suggest that clinically relevant, multisession ABM intervention might reduce symptoms problem rating, as well as frequency of symptoms in women experiencing troublesome menopausal symptoms. Further research is however warranted to delineate these findings.

Regarding the exploratory objective of this study, a number of conclusions need to be drawn. Post-ABM interviews with women that finished the 4 sessions of training, as well as on the spot observations, revealed that none of the women felt that the task was engaging. Moreover they felt that it was boring, tiring and too long. Also, they found it difficult to attend to 4 sessions of ABM, transportation and time resources representing a main concern. Most of them expressed the need for a more attractive and engaging "computer game", thus suggesting that a friendlier interface of the task would be helpful in terms of engaging and attendance to the session. However, thirteen out of fifteen initial participants completed the 4 sessions of ABM.

Given these preliminary findings we conclude that there is a good possibility of integrating an ABM intervention in the context of ambulatory chemotherapy, as long as the intervention is delivered on the day of the patient's treatment. In building such an intervention, two aspects should be of paramount importance: 1) duration of intervention and 2) circumstances in which the intervention is delivered.

STUDY 3: Attentional bias and response expectancies in breast cancer patients undergoing chemotherapy: An exploratory study[3]

Introduction

Considering the large impact of emotional distress on the experience of cancer diagnosis and treatment, the assessment of psychological predictors of distress becomes highly important. For breast cancer patients, predictors of depression and anxiety seem to be related to the patient's psychosocial vulnerabilities (i.e., previous psychological problems, lack of an intimate confiding relationship, and experience of severe non-cancer difficulties (Burgess et al., 2005) rather than to the disease or treatment. One other area with potential explanatory role could be individual trait factors involved in the subjective perception of the breast cancer treatment experience.

The cognitive-behavioral therapy (CBT) framework (Beck, 1976; Ellis, 1994) stipulates that individuals have specific cognitive schemata through which they interpret life events/experiences, and which, if distorted (i.e., dysfunctional), may lead to the development of clinical symptoms. Hence, we can assume that the cognitive style of a patient can influence subsequent interpretations of their medical condition or related symptoms, and consequently can lead to psychological distress. One of the most influential cognitive construct that has been shown to influence psychological distress is represented by irrational beliefs (IBs), the central construct in rational-emotive and cognitive-behavioral theory (REBT; Ellis, 1994).

More closely related to the context of treatment, a specific cognitive style regarding the experience of somatic sensations – the *amplifying somatic style* has been described in the literature (Barsky, 1992; Barsky et al., 1999). It involves the tendency to fear bodily sensations, catastrophic beliefs about the implications of these sensations and the tendency to be hypervigilent for, and focus on, bodily sensation, even if they are weak sensations. Similarly, it involves a focus on disease related information (Taylor & Asmundson, 2004).

Moreover, Clark, Beck, and Brown (1989) have shown that maladaptive beliefs are predicted to result in cognitive biases favoring self-congruent negative information. In this sense, attentional biases (i.e., preferentially allocate attention to self-congruent stimuli when they compete for attentional resources with neutral stimuli) have been associated with emotional disorders (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007; Beck & Clark, 1997; Donaldson, Lam, & Mathews, 2007). Recently, an increasing number of studies have started to examine attentional biases towards pain (Schoth, Nunes, & Liossi, 2012), gastro-intestinal symptoms (Afzal, Potokar, Probert, & Munafò, 2006) and idiopathic environmental intolerance symptoms (Skovbjerg, Zachariae, Rasmussen, Johansen, & Elberling, 2010), suggesting that, in the presence of a health

[3] Parts of this study have been published, as follows: Cobeanu, O. (2013). Attentional bias and treatment related symptoms in breast cancer patients undergoing chemotherapy: preliminary results of an exploratory study, *Transilvanian Journal of Psychology*, *14*(1); Cobeanu, O. (2013). Irrational beliefs and somatosensory amplification in breast cancer patients undergoing treatment: impact on general distress. *Journal of Cognitive and Behavioral Psychotherapies*, *13* (2a).

condition, selective attentional processing of somatic stimuli is also a constant feature and can be associated with poorer levels of general functionality, emotional functionality and health associated behaviors.

The first aim of the present study was to investigate attentional bias (AB) towards chemotherapy symptoms, additionally considering other psychological variables, known to be involved in the experience of these symptoms. Also, in an exploratory manner, we investigat**e** the relation between IBs and SAS in regard to their possible influence on distress experienced by breast cancer patients undergoing chemotherapy.

Methods

Design and statistical methodology

We used a predictive correlational design. To statistically analyze the data, we used correlations and linear regression.

Participants

Thirty breast cancer patients were recruited from an oncological private clinic. All participants were undergoing chemotherapy and received standard antiemetic adjuvant treatment. After expressing their consent, they were asked to fill in a battery of psychological tests. Prior to their chemotherapy session, they completed the AB task.

Measures

Chemotherapy symptoms measures.

Chemotherapy symptoms (i.e., nausea, vomiting, pain and fatigue) were measured post-chemotherapy using 10-cm *Visual Analogue Scales* (VASs). This approach has shown good reliability in multiple studies (e.g., Montgomery & Bovbjerg, 2004; Montgomery & Kirsch, 1997).

Emotional distress measures.

The Profile of Mood States-Short Version (POMS-SV; Shacham, 1983) is a 47-item instrument that measures the intensity of general emotional distress.

Cognitive measures.

The Attitudes and Beliefs Scale (ABS-II; DiGiuseppe, Leaf, Exner, & Robin, 1988) measures irrational cognitions (demandingness, global evaluation/self-downing, low frustration tolerance, and awfulizing), as well as their rational counterparts (preferential thinking, unconditional self-acceptance, frustration tolerance, and non-awfulizing). The *Somatosensory Amplification Scale* (SSAS; (Barsky, Wyshak, & Klerman, 1990) assesses the tendency to experience ordinary bodily and visceral sensation as intense, noxious, and disturbing. *Response expectancies* for nausea, vomiting, pain and fatigue were measured also using 10-cm VASs.

AB Assessment Task.

We used a version of the dot-probe task (MacLeod, Mathews, & Tata, 1986) to measure AB. Each trial began with a central fixation cross, presented for 500 ms. After this interval, two stimuli were presented for another 500 ms on the computer screen, above and below from the previous presented fixation cross. One of the stimuli was symptom-related, while the other one was neutral. After their removal, a neutral cue (letter „E" or „F") appeared in one of the locations previously occupied by the two stimuli. Participants were asked to identify the letter on the screen (by pressing the corresponding computer key). They were instructed to answer as quickly and accurate as possible. The letter remained on the screen until the participant made her response. Reaction time (RT) data were collected for every trial. We used linguistic stimuli, based on qualitative interviews run with breast cancer patients that had already finished their chemotherapy sessions. Similar to Afzal and colleagues (2006), we selected our neutral stimuli mainly from "household" Romanian words matched for length with the symptom-related words. We used a total 18 symptom-related words, and 18 neutral words. Participants completed a total of 144 trials.

Procedure

Patients were recruited on the day of their chemotherapy session. Inclusion criteria were a diagnostic of breast cancer and an ongoing chemotherapy regimen. Women who expressed interest in the study were asked a few questions to determine eligibility. Those who met the inclusion criteria were informed about the purpose of the study and given consent forms. The study was presented as an investigation of how attention skills relate to the experience of treatment. On the day of their next chemotherapy session, they completed self-administered questionnaires. Prior to the chemotherapy session they completed the AB computerized task, along with the VAS for the assessment of response expectancies towards symptoms. After the chemotherapy session they completed also the VAS for secondary symptoms to chemotherapy (i.e., nausea, vomiting, pain and fatigue).

Results

Relations between attentional bias and hypothesized variables.

Seventeen of the participants (60.7%) obtained positive bias scores, while eleven (39.3%) obtained negative bias scores.

We did not find any significant correlation between AB and the variables considered. General irrationality was a significant predictor of distress pre-chemotherapy session, $F(1,28) = 9.808$, $p = 0.004$, $R^2 = .259$, $\beta = .509$. Response expectancies for nausea significantly predicated nausea reported post-chemotherapy, $F(1,28) = 12.316$, $p = 0.002$, $R^2 = .305$, $\beta = .553$.

Exploratory post-hoc analysis

Relations between somatosensory amplification style and irrational beliefs

Correlation and mediation analysis were performed. For mediation analysis, we used the bootstrapping procedure for assessing indirect effects (Preacher & Hayes, 2008). Preacher and Kelley's (2011) kappa-square (i.e., k^2) was reported as effect size for the mediation model, as well as corresponding confidence intervals.

Correlations between variables are presented in Table 1. For mediation analysis, we used bootstrapping tests with 5000 re-samples and the bias corrected confidence interval (Preacher & Hayes, 2008).

Table 1. *Correlations between variables*

	IBs	SAS	D
IBs	1	.436*	.409*
SSAS		1	.561**
D			1

Note: IBs = Irrational Beliefs (DiGiuseppe, Leaf, Exner, & Robin, 1988); SAS = Somatosensory Amplification Style (Barsky et al., 1990); D = Distress (positive and negative affectivity) (Shacham, 1983); *$p < 0.05$, **$p < 0.01$

We found no evidence of a mediating effect of IBs on the relationship between SAS and distress, indirect effect = 0.206, SE = 0.328, 95% CI = [-0.153; 1.343], k^2 = 0.103, 95% CI = [0.002; 0.402]. Moreover, the results (see Figure 2) showed that somatosensory amplification significantly mediated the relationship between IBs and distress, indirect effect = 0.204, SE = 0.131, 95% CI = [0.011; 0.543], k^2 = 0.206, 95% CI = [0.032; 0.477]. The direct effect (c' = 0.2) was not statistically significant (p = 0.233). In relation to this result, we calculated the proportion of the total effect that is mediated (i.e., the indirect effect divided by the total effect), considering that the value of the standardized c (c = .405) respected the recommendations of Kenny, Kashy and Bolger (1998) (i.e., $c \geq .2$). The results showed that 50% of the total effect is explained by the mediator.

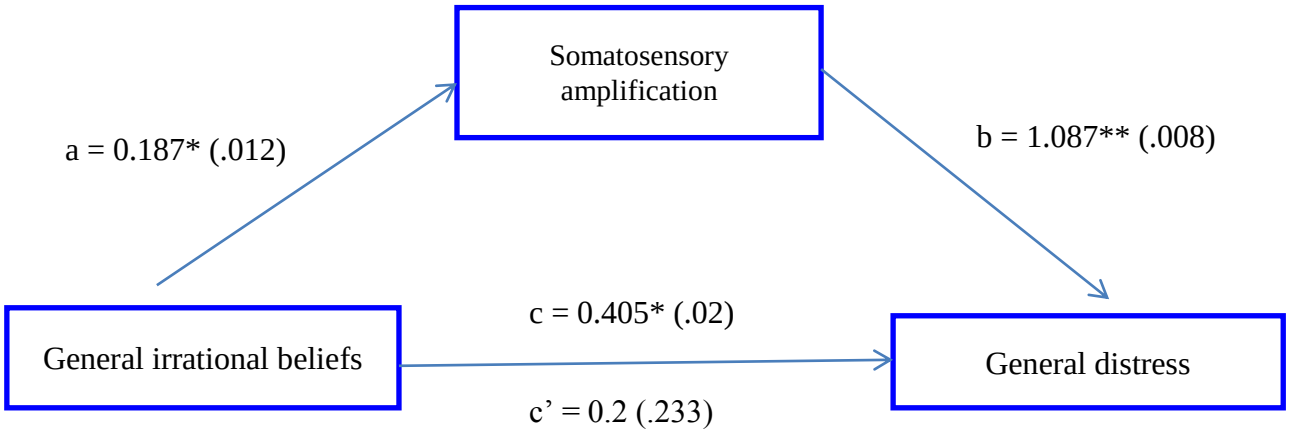

Figure 1. Simple mediation diagram. Values are path coefficients representing unstandardized regression coefficients and standard errors (in parentheses); *p < 0.05; **p < 0.01

Discussion

Only seventeen patients showed an AB towards chemotherapy symptoms. As this study is the first to investigate the presence of this particular AB in breast cancer patients undergoing chemotherapy, several implications are in line. It may be possible that AB is not a definite feature of this patients or/and it may be influenced by other psychological individual particularities. Secondly, AB did not correlate with self-reported chemotherapy symptoms. We could not find any significant correlation between irrationality, response expectancies, distress and AB. The small sample size could account for this lack of findings and further research should attempt to reconsider this hypothesis on larger samples.

We found that the effect of SAS on pre-chemotherapy distress was not accounted for by IBs. Rather, SAS had a mediating role in the relationship between IBs and distress experienced prior to the chemotherapy session, in breast cancer patients, accounting for 50% of the total effect. The mediating role played by more specific (i.e. to particular stressful situations) constructs, like *response expectancies* and *automatic thoughts*, in the relationship between IBs and distress, has already been validated (Montgomery, David, Dilorenzo, & Schnur, 2007; Szentagotai & Freeman, 2007; Vîslă, Cristea, Szentágotai Tătar, & David, 2013). Similarly, somatosensory amplification beliefs, more relevant to the context of treatment and/or of a life-threatening disease, mediate between IB and distress pre-chemotherapy, in breast cancer patients. Based on these results, it is possible to assume that interventions which address both IBs (e.g., REBT; Ellis, 1994) and SAS (e.g., CBT protocols that target health anxiety related beliefs; (Taylor & Asmundson, 2004) may be efficacious in treating cancer treatment related distress.

Study 4: Attention bias modification and relaxation interventions in breast cancer patients undergoing chemotherapy: preliminary results of a randomized clinical trial

Introduction

Research has shown that breast cancer patients experience heightened psychological distress during their course of chemotherapy. Among the factors that may contribute to patients' emotional distress are the physical effects of the treatment: nausea, vomiting, diarrhea, general debility, alopecia, loss of taste, appetite, and sexual function. Moreover, the number of side effects experienced, but not their duration or severity, seems to be positively correlated with distress; similarly, constant side effects such as tiredness and pain seem more likely to be associated with distress than acute, specific side effects such as nausea and vomiting (Nerenz, Leventhal, & Love, 1982). The impact of side effects on distress lasts even after the end of chemotherapy. Jim et al. (2007) have shown that greater physical symptoms/side effects experienced during adjuvant treatment (i.e., chemotherapy, radiotherapy or both) predict greater total cancer-related distress, intrusive thoughts, and general distress, at 4 months following the end of a course of treatment.

This relation between distress and the experience of side effects, during a course of breast cancer treatment, can be explained, in the cognitive-behavioral framework (Beck, 1976; Ellis, 1994), by common cognitive mechanisms (i.e., dysfunctional beliefs), like symptoms catastrophizing and low frustration tolerance in regards to the treatment regimen.

As cognitive-behavioral interventions for side-effects of treatment and associated distress, in breast cancer patients, undergoing treatment, show a small effect, we believe that research should be developed in what concerns cognitive mechanisms that might be addressed in order to increase CBT's efficacy in the specific context of breast cancer treatment.

The aims of the present randomized clinical trial were (1) to investigate the efficacy of an ABM enhanced CBT protocol, compared to a CBT protocol alone, on subjective reports of side effects of chemotherapy and distress, during breast cancer treatment and (2) investigate the effect of an ABM enhanced CBT protocol, compared to a CBT protocol alone, on attention bias and response expectancies for side effects of chemotherapy. We have run exploratory analyses on (1) the efficiency of the ABM enhanced CBT protocol, as opposed to a CBT protocol alone, in reducing symptoms catastrophizing, and on (2) the efficiency of the ABM training alone in reducing response expectancies for side effects and distress.

Methods

Design and Statistical Methodology

We used an experimental design. The independent variable was the type of intervention delivered. Participants were randomized in two groups: (1) CBT intervention alone or (2) ABM enhanced CBT.

As dependent variables, we measured (1) side effects of chemotherapy and distress, as primary outcomes, (2) quality of life, as secondary outcome, and (3) attention bias towards side effects of chemotherapy, response expectancies for distress and side effects of chemotherapy (i.e., nausea, vomiting, fatigue and pain), and symptoms catastrophizing (exploratory analysis), as mechanisms of change. In addition, to control for possible differences between groups, we measured the following variables at baseline: irrational and rational beliefs, automatic thoughts, attention control, cancer specific beliefs, somatosensory amplification style, general distress and depressive symptomatology.

Participants

We included 47 breast cancer patients (mean age: 51.45, standard deviation: 10.08), recruited from the Ion Chiricuta Oncological Institute, in Cluj-Napoca. Recruitment and enrollment in the study were conducted on a continuous basis, over a six months period (April to October 2013). Eligibility criteria involved a breast cancer diagnosis, starting a chemotherapy regimen (i.e., no other previous experience with chemotherapy), no metastasis, no other physical or psychiatric conditions that would affect their participation in the study, and a good understanding of the Romanian language. Fifty-seven patients were referred by the medical stuff, out of whom 54 were eligible. Of those, 47 patients volunteered to take part in the program (see Figure 1) and were randomly allocated to one of the intervention group.

Measures

Baseline measures.

The General Attitudes and Beliefs Scale (GABS; Lindner, Kirkby, Wertheim, & Birch, 1999) measures irrational and rational beliefs. *The Automatic Thoughts Questionnaire* (ATQ; Hollon & Kendall, 1980) is a 15-item instrument that measures the frequency and of negative self-statements associated with depression. *The Attentional Control Scale* (ACS; Derryberry & Reed, 2002) is a 20-item scale, that evaluates the person's ability of flexibly use attentional resources for the task (s) he is involved in despite distractors and/or for tasks that requires frequent attentional switches. *The Impact of Events Scale* (IES; Horowitz, Wilner, & Alvarez, 1979) is a 15-item self-report instrument assessing degree of thought intrusion and avoidance about particular life situations (here the diagnosis of and treatment for breast cancer), The *Somatosensory Amplification Scale* (SSAS; Barsky et al., 1990) is a 10-item self-report questionnaire assessing the tendency to experience ordinary bodily and visceral sensation as intense, noxious, and disturbing. *The Profile of Mood States-Short Version* (POMS-SV; Shacham, 1983) is a 47-item instrument that measures the intensity of general emotional distress (positive and negative affectivity). The level of depression was assessed with *The Beck Depression Inventory - Second Edition* (BDI-II; Beck, Steer, Ball, & Ranieri, 1996; Beck, Steer, & Brown, 1996).

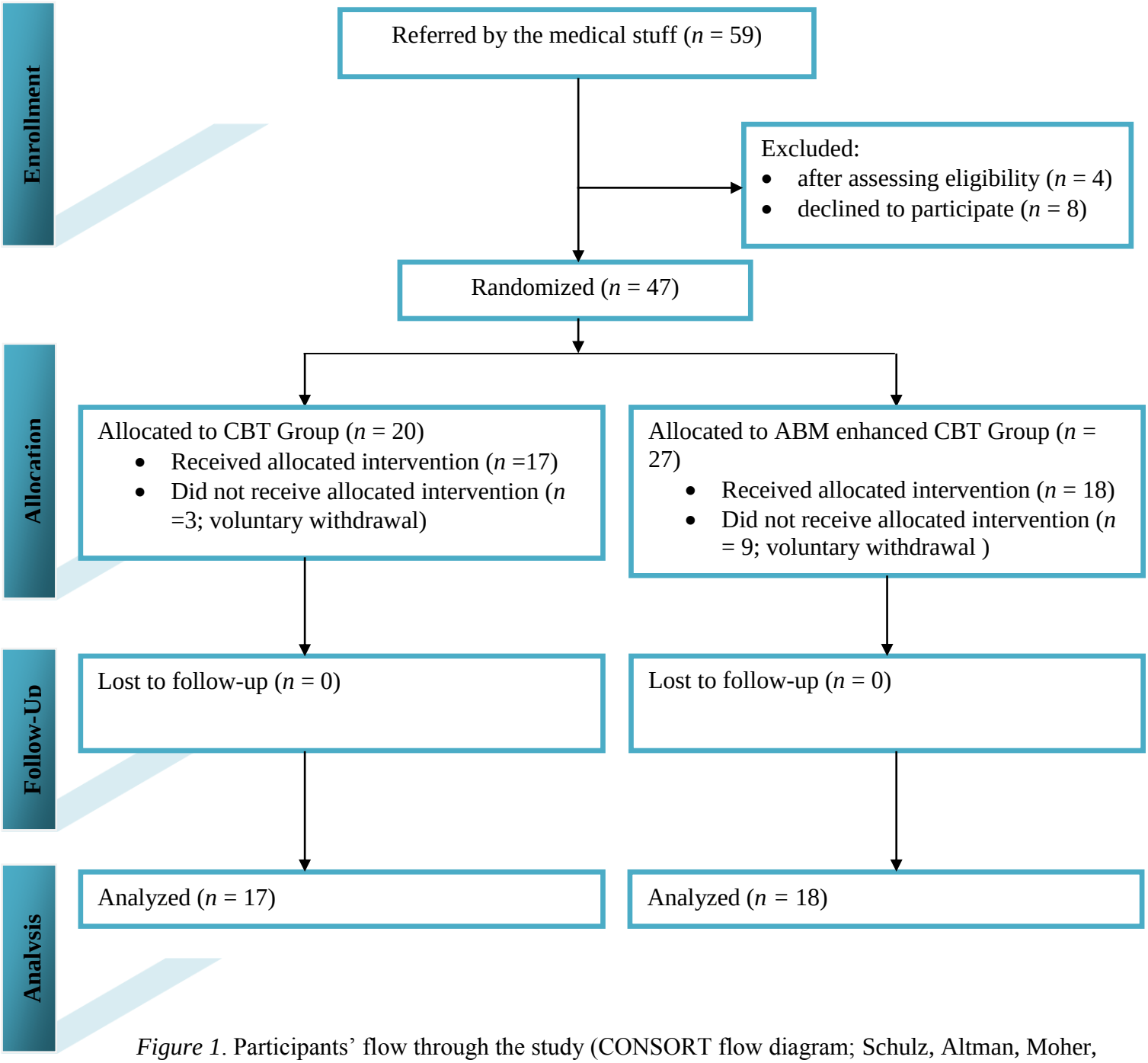

Figure 1. Participants' flow through the study (CONSORT flow diagram; Schulz, Altman, Moher, & for the CONSORT Group, 2010)[1]

Primary and secondary outcomes.

Chemotherapy symptoms (i.e., nausea, vomiting, pain and fatigue) were measured post-chemotherapy using 10-cm *Visual Analogue Scales* (VASs). Symptoms and quality of life were also measured with the *European Organisation for Research and Treatment of Cancer QLQ-C30 Questionnaire* (EORTC-QLQ30; (Aaronson et al., 1993). Distress was measured with the *The Profile of Mood States-Short Version* (POMS-SV; Shacham, 1983).

Mechanisms of change measures (self-report).

Response expectancies for nausea, vomiting, pain and fatigue were measured also using 10-cm VASs. *The Symptoms Catastrophizing* assesses the tendency to catastrophize treatment secondary symptoms. It was adapted after the *Pain Catastrophizing Scale* (Sullivan, Bishop, & Pivik, 1995).

Attention bias assessment task and the ABM task

We used the same procedure as in Study 3. Stimuli used for both assessment and ABM task were based on the 36 stimuli obtained also in Study 3. However, we excluded stimuli composed out of two words, in order to improve the task (i.e., by eliminating possible two long reactions times). Finally, we have included 14 words in the assessment task and another 14 in the training task. We used the same neutral stimuli as in Study 3, and added another 14, following the procedure of Afzal et al. (2006).

CBT intervention protocol

The rationale provided for the CBT intervention was that it has already been demonstrated to be effective for controlling symptoms associated with cancer and its treatment. The intervention (adapted after Montgomery et al., 2009), a brief 15 minute relaxation session, consisted of (1) a hypnotic induction including suggestions for mental and physical relaxation; (2) guided imagery of a peaceful and safe place; (3) suggestions for increased hypnotic depth; (4) and specific suggestions for reduced chemotherapy-related fatigue, nausea, vomiting and pain, reduced distress, increased sense of relaxation, increased well-being, and increased energy. Following these suggestions, patients were given a cue word for entering hypnosis on their own. The interventionist then ended the session.

Procedure

Patients were approached at the beginning of their chemotherapy regimen. The intervention was described as being part of a psychological support program during chemotherapy, developed in order to help patients manage better the side effects of treatment. They were approached at their first chemotherapy session, given informed consent forms and first pack of questionnaires, to bring at their next session of chemotherapy, if deciding to participate in the study. Enrollment took place at the second session of chemotherapy. Patients were then randomly allocated to one of the intervention group.

On the day of their second chemotherapy session they completed measures of emotional distress, quality of life and side effects of chemotherapy, experienced during the week before. Before the chemotherapy session the interventionist met with each patient in a private room at the Clinical Psychology Unit of the Babeș-Bolyai University (in the immediate vicinity of the Oncological Institute) to conduct a brief 15 minutes relaxation session and an attentional control task.

Prior and post to the psychological intervention, measures of AB and response expectancies for side effects of chemotherapy were administered. After the chemotherapy session, visual analogue scales (VASs) for side effects of treatment (i.e., nausea, vomiting, fatigue, and pain) and distress were also administered. Follow-up data (i.e., same questionnaires administered prior to the psychological intervention) was collected one week later.

Results

Means and standard deviations for controlled variables at baseline are shown in Table 1. No significant differences between groups were evidenced.

Table 1. *Means (M) and standard deviation (SD) for measures of controlled variables*

	Group 1: CBT Relaxation (n = 17)	Group 2: ABM enhanced CBT relaxation (n = 18)	One way ANOVA
GABS IR	65.78 (11.65)	61.27(13.36)	$F(1, 39) = 1.309$; $p = 0.260$; $\eta^2 = .032$
GABS R	15.89(1.41)	16.36(1.64)	$F(1, 39) = .941$; $p = 0.338$; $\eta^2 = .024$
ATQ Frequency	27.44 (9.38)	26.47 (13.48)	$F(1, 39) = .067$; $p = 0.797$; $\eta^2 = .002$
ATQ Credibility	30.82 (14.06)	35.31 (19.99)	$F(1, 39) = .562$; $p = 0.459$; $\eta^2 = .018$
IES	30.33(11.90)	30.58(15.01)	$F(1, 33) = .003$; $p = 0.956$; $\eta^2 = .000$
SSAS	30.80 (5.65)	31.15 (7.16)	$F(1, 38) = .029$; $p = 0.865$; $\eta^2 = .001$
ACS	46.41(6.06)	44.22(6.90)	$F(1, 33) = .989$; $p = 0.327$; $\eta^2 = .029$
Negative and positive affectivity POMS	57.00(23.83)	50.20(21.26)	$F(1, 21) = 2.297$; $p = 0.145$; $\eta^2 = .099$
BDI	12.00 (4.85)	12.33 (11.70)	$F(1, 37) = .013$; $p = 0.911$; $\eta^2 = .000$

Note: GABS IR = The General Attitudes and Beliefs Scale (Lindner et al., 1999), Irrationality subscale; GABS R = The General Attitudes and Beliefs Scale (Lindner et al., 1999) Rationality subscale;

ATQ = The Automatic Thoughts Questionnaire (Hollon & Kendall, 1980); IES = The Impact of Events Scale (Horowitz et al., 1979); SSAS = The Somatosensory Amplification Scale ((Barsky et al., 1990); ACS = The Attentional Control Scale (Derryberry & Reed, 2002); BDI = The Beck Depression Inventory - Second Edition (Beck, Steer, Ball, et al., 1996; Beck, Steer, & Brown, 1996).

Intervention effect on primary and secondary outcomes

Means and standard deviations for primary and secondary outcome measures are shown in Table 2. Analysis of covariance (ANCOVA) conducted on the side effects ratings, while controlling for baseline levels, revealed no differences between groups. Similarly, ANCOVA conducted on the distress ratings and quality of life measures respectively evidenced no differences between groups.

Table 2. *Means (M) and standard deviation (SD) for measures of primary and secondary outcomes, and differences between groups at post-intervention (i.e., one week after chemotherapy)*

	Group 1: CBT Relaxation	Group 2: ABM enhanced CBT relaxation	ANCOVA
Nausea and Vomiting EORTQ	42.22 (20.76) (*n* =15)	32.40 (24.56) (*n* =18)	$F(1, 30) = 1.628$; $p = .212$; $\eta^2 = .051$
Fatigue EORTQ	48.61 (20.63) (*n* =16)	47.53 (21.82) (*n* =18)	$F(1, 31) = .106$; $p = .747$; $\eta^2 = .003$
Pain EORTQ	27.08(19.12) (*n* =16)	18.62(21.95) (*n* =17)	$F(1, 30) = .795$; $p = .380$; $\eta^2 = .026$
Side effects EORTQ	46.66 (15.71) (*n* =15)	39.58 (12.38) (*n* =16)	$F(1, 28) = 1.212$; $p = .280$; $\eta^2 = .041$
Anxiety POMS	7.30(4.62) (*n* =13)	7.76(6.31) (*n* =17)	$F(1, 27) = 2.424$; $p = .131$; $\eta^2 = .082$
Depression POMS	15.10(8.86) (*n* =10)	11.00(15.24) (*n* =15)	$F(1, 22) = 1.328$; $p = .261$; $\eta^2 = .057$
Global Functioning EORTQ	37.5(13.37) (*n* =14)	45.37(15.45) (*n* =18)	$F(1, 29) = 2.685$; $p = .112$; $\eta^2 = .085$

One way analysis of variance (ANOVA) conducted on the side effects ratings (i.e., measured using visual analogue scales) immediately after the chemotherapy session revealed no differences between groups, with the exception of pain ratings. When controlling for levels of pain experienced one week prior to the chemotherapy session, the results remained significant, $F(1, 31) = 5.510$, $p = .025$, $\eta^2 = .151$.

Intervention effect on presumed mechanisms of change

Intervention effect on attentional bias

Analysis of covariance (ANCOVA) conducted on the attentional bias scores at post-intervention, while controlling for baseline levels, revealed no differences between groups, $F(1, 27) = 1.131$, $p = .297$, $\eta^2 = .040$.

A 2 (Time: Pre and post Intervention) x 2 (Group: CBT, ABM enhanced CBT) ANOVA with repeated measures conducted on the attentional bias scores revealed a non-significant main effect of time, $F(1, 28) = 1.054$, $p = .313$, $\eta^2 = .036$, a non-significant main effect of group, $F(1, 28) = .091$, $p = .766$, $\eta^2 = .003$, and a non-significant effect of Time x Group, $F(1, 28) = 2.423$, $p = .131$, $\eta^2 = .080$.

Intervention effect on response expectancies

Analysis of covariance (ANCOVA) conducted on the same variables ratings, while controlling for baseline levels, revealed no differences between groups, at post-intervention, with the exception of response expectancies for pain, $F(1, 32) = 5.962$, $p = .020$, $\eta^2 = .157$, which were significantly lower in the ABM enhanced intervention group. However, change in response expectancies for pain did not correlate with levels of pain measured immediately after the chemotherapy session, $r(18) = .218$, $p = 0.386$, or change in levels of pain from pre-intervention to one week post-intervention, , $r(16) = .148$, $p = 0.584$.

Exploratory post-hoc analyses

Intervention effect on symptoms catastrophizing

Analysis of covariance (ANCOVA), controlling for baseline scores, showed no significant differences between groups at post-intervention regarding symptoms catastrsophizing, $F(1, 27) = .011$, $p = .917$, $\eta^2 = .000$.

A 2 (Time: Pre and post Intervention) x 2 (Group: CBT, ABM enhanced CBT) ANOVA with repeated measures conducted on symptoms catastrophizing scores revealed a non-significant main effect of time, $F(1, 28) = 1.945$, $p = .174$, $\eta^2 = .065$, a non-significant main effect of group, $F(1, 28) = 2.258$, $p = .144$, $\eta^2 = .075$, and a non-significant effect of Time x Group, $F(1, 28) = .091$, $p = .765$, $\eta^2 = .003$.

Effect of the ABM intervention alone on response expectancies

Paired t tests confirmed the presence of significant differences pre – post ABM intervention alone between response expectancies for nausea, $t(17) = 3.229$, $p = .005$, fatigue, $t(17) = 3.276$, $p = .004$ and distress, $t(17) = 2.925$, $p = .009$.

Discussion

This study aimed (1) to exploratory investigate the efficacy of an ABM enhanced CBT intervention, compared to a CBT intervention alone, on subjective reports of side effects of chemotherapy and distress, during breast cancer treatment and (2) investigate the effect of an ABM enhanced CBT intervention, compared to a CBT intervention alone, on attention bias and response expectancies for side effects of chemotherapy. We have run supplementary exploratory analyses (1) on the efficiency of the ABM enhanced CBT intervention, as opposed to the CBT intervention alone in reducing symptoms catastrophizing, and (2) on the ABM training alone in reducing response expectancies for side effects of chemotherapy and distress.

First, we found no significant differences between the two intervention groups effects on outcomes considered, with the exception of pain measured immediately after chemotherapy. The ABM enhanced CBT intervention seemed to lead to lower levels of pain,

post-chemotherapy, as opposed to the CBT intervention alone, even when controlling for levels of pain experienced one week prior to the chemotherapy session.

Second, we found no significant differences between groups in what concerns the considered mechanisms of change, with the exception of response expectancies for pain. Again, the ABM enhanced CBT intervention seemed to lead to lower response expectancies for pain, as opposed to the CBT intervention alone. However, change in response expectancies for pain did not correlate with pain experienced post-chemotherapy session, thus indicating the absence of a clear relation between mechanisms of change considered by us and the effect of the intervention on pain.

Further on, regarding exploratory analyses, we found that response expectancies for nausea, fatigue and distress seem to be reduced after the ABM training alone (i.e., additionally to measuring pre-post intervention response expectancies, in the ABM enhanced CBT intervention we also measured response expectancies before and after ABM). This finding points to a possible effect of ABM on response expectancies. However, as we did not have a control group, this hypothesis needs further investigations. The supplementary exploratory analysis on effects of the interventions on symptom catastrophizing, showed no significant differences between the two groups and no effect of time.

To summarize, our results do not support the superiority of an ABM enhanced CBT intervention, in reducing side effects of treatment and distress. Still, this was an exploratory one-session intervention trial, thus we can't conclude that ABM cannot bring increased efficiency in an extended version (i.e., multiple sessions). Despite its mainly negative findings, this study brings new information on ABM research, extended to a new population (i.e., breast cancer patients). Although we cannot draw firm conclusions, ABM enhanced CBT for breast cancer patients might be potentially efficacious or at least as good as a CBT intervention alone.

CHAPTER IV. GENERAL CONCLUSIONS AND IMPLICATIONS

The aim of this research project was to investigate within a CBT perspective the role that response expectancies and attentional bias play together in the generation of emotional and physical distress experienced by breast cancer patients undergoing chemotherapy. The effect of response expectancies on medical treatments related side effects has been shown in a number of researches, developed in the cancer treatment domain (Montgomery & Bovbjerg, 2000, 2004). We now know that they play a central role in the generation of non-volitional outcomes like side effects of treatment and associated distress (Montgomery & Bovbjerg, 2000; Montgomery et al., 2010; Sohl et al., 2009). Further on, recent research on attentional biases toward physical symptoms in several health conditions (Afzal et al., 2006; Boston & Sharpe, 2005; Hou et al., 2008; Karademas et al., 2008; Skovbjerg et al., 2010) has determined as to consider the role of an attentional bias towards side effects of chemotherapy.

To this point, research regarding attentional biases in cancer patients has considered only general threat or cancer related information. Hence, we decided to integrate and expand this research inside the CBT framework, and especially in relation to response expectancies for side effects of treatment. Moreover, we were also interested in the clinical implications of this fundamental research, aiming at possible enhancement of existing CBT protocols designed for the management of side effects and distress during cancer treatment. We started our research with a systematic review on CBT interventions for side effects and distress, in breast cancer patients undergoing neo-adjuvant or adjuvant treatments, which subsequently guided our strategy in building an enhanced CBT intervention.

Previous to this final goal, we piloted the use of a computerized task (i.e., dot-probe task) for the measurement and retraining of attentional bias, on a population similar to the one of breast cancer patients. Then we proceeded to the investigation of attentional bias towards side effects of chemotherapy and response expectancies in breast cancer patients undergoing chemotherapy. Finally, we have built an attentional bias modification (ABM) intervention, which was added to a standard CBT protocol (i.e., relaxation intervention) designed for the management of side effects and distress in breast cancer patients. Within a randomized clinical trial, we investigated the efficacy of this new enhanced protocol compared with the standard one. Several theoretical and conceptual advances along with some methodological innovations are worth mentioning here.

4.1. Theoretical and conceptual advances

The main objective of our research was to investigate the role that response expectancies and attentional bias for side effects of chemotherapy play together in the generation of emotional and physical distress experienced by breast cancer patients undergoing chemotherapy, within a CBT framework. Clinical implications of this relation were also considered, in order to enhance existent CBT protocols. Our first study, the systematic review on cognitive behavioral interventions (CBI) for side effects and distress in breast cancer patients undergoing treatment revealed a small, but significant effect of CBI on side effects of treatment, overall distress and quality of life at post-treatment and also at follow-up. When analyzing specific side effects outcomes, we found that CBI are efficient in reducing patients' nausea and vomiting, but not their fatigue, pain or sleep disturbances, during treatment. CBI had a small, but significant effect on anxiety. We did not find a significant effect of CBI in addressing depressive symptomatology reported by breast cancer patients. We found no significant moderators for the effect of CBI on any of the outcomes considered in the moderation analysis. However, a trend regarding type of

therapy (i.e., individual vs. group therapy) emerged in relation to overall distress. A similar trend emerged when considering the CBI main component as a moderator of CBI effect on the overall treatment side effects: patients receiving behavioral interventions seem to report less intense and/or frequent side effects of treatment. In the context of acute treatment, behavioral interventions (e.g., relaxation exercises, stimulus control) may be more likely to register a positive effect on side effects of treatment than cognitive-behavioral interventions. Information provided by our study can be used in the development of interventions for breast cancer patients undergoing treatment. However, further research is necessary in identifying more efficient cognitive-behavioral protocols for specific side effects like pain, fatigue and sleep disturbances, during breast cancer treatment.

Consequently, the second and third study aimed at investigating mechanisms that might contribute to the enhancement of existing CBT protocols, along with piloting new interventions protocols. We concluded that there is a good possibility of integrating an ABM intervention in the context of ambulatory chemotherapy, as long as the intervention is delivered on the day of the patient's treatment. In building such an intervention, we considered two aspects to be of paramount importance: 1) duration of intervention and 2) the circumstances in which the intervention is delivered.

Regarding theoretical developments, we did not find a significant relationship between attentional bias (AB) towards side effects of chemotherapy and the actual experience of symptoms. However, AB seems to be positively correlated (yet not significantly) with general distress and response expectancies for chemotherapy symptoms (i.e., nausea, vomiting, fatigue and pain). Also, we could not find any significant correlation between irrationality and AB. The small sample size could account for this lack of findings and further research should attempt to reconsider this hypothesis on larger samples.

Further on, response expectancies for nausea significantly predicted nausea experienced post-chemotherapy. This finding replicates previous research results (Montgomery & Bovbjerg, 2004). Also, general irrationality significantly predicted distress prior to the chemotherapy session, sustaining previous findings consistent with the cognitive-behavioral paradigm (Montgomery, David, Dilorenzo, & Schnur, 2007). Together with general irrationality, response expectancies for nausea should be considered when building psychological intervention protocols for breast cancer patients undergoing chemotherapy. In the same context, we found that the somatosensory amplification style (SAS) had a mediating role in the relationship between IBs and distress experienced prior to the chemotherapy session, in breast cancer patients, accounting for 50% of the total effect. These findings add to the previous body of research on the relationship between IBs and distress. The mediating role played by more specific (i.e. to particular stressful situations) constructs, like response expectancies and automatic thoughts, in the relationship between IBs and distress, has already been validated (Montgomery et al., 2007; Szentagotai & Freeman, 2007; Vîslă et al., 2013). Similarly, somatosensory amplification beliefs, more relevant to the context of treatment and/or of a life-threatening disease, mediate between IB and distress pre-chemotherapy, in breast cancer patients.

Based on these results, it is possible to assume that interventions which address both IBs (e.g., REBT; Ellis, 1994) and SAS (e.g., CBT protocols that target health anxiety related beliefs; Taylor & Asmundson, 2004) may be efficacious in treating cancer treatment related distress. Within an experimental design, the effects of manipulating IBs and SAS, through an integrative CBT protocol, could provide more sound evidence for the meditational model identified through our research.

Finally, we considered a number of limitations that might have accounted for the absence of a significant relation between AB and considered variables. Out of these, we addressed in our final study a limitation related to the AB assessment task. We had used longer linguistic stimuli than usual standard dot-probe tasks, as some of the chemotherapy symptoms were described with two-word expressions (e.g., iron taste). This might have affected the implicit understanding of the stimuli, as exposure time for trials did not differ as a function of word/expression length. Consequently, we removed the longer linguistic stimuli (for Study 4) and used only one word stimuli.

Our last study (Study 4) was aimed (1) to investigate the efficacy of an ABM intervention plus relaxation, compared to relaxation only, on subjective reports of side effects of chemotherapy and distress, during breast cancer treatment and (2) investigate the effect of an ABM intervention plus relaxation, compared to relaxation only, on attention bias and response expectancies for side effects of chemotherapy. Once again, we did not find any significant relation between attentional bias and any of the considered variables. Also, our results did not support the superiority of an ABM enhanced CBT relaxation intervention, in reducing side effects of treatment and distress. Still, this was an exploratory one-session intervention trial, thus we can't conclude that ABM cannot bring increased efficiency in an extended version (i.e., multiple sessions).

4.2. Methodological innovations

The main objective of this research was to investigate the role that response expectancies and attentional bias for side effects of chemotherapy play together in the generation of emotional and physical distress experienced by breast cancer patients undergoing chemotherapy, within a CBT framework. In order to reach this objective, we first developed an attentional bias towards side effects of chemotherapy assessment task, using a qualitative approach. We ran qualitative interviews with breast cancer patients that had already finished their chemotherapy sessions. We asked 20 women undergoing radiotherapy at the Oncological Institute in Cluj-Napoca to freely write down all words they thought described secondary symptoms to chemotherapy. After the pools of potential stimulus words had been collected, we retained only the words that had a frequency higher than 3. The final list contained 36 chemotherapy symptoms related words, out of which we have randomly selected 18 for the assessment task, and the other 18 for the ABM task. Eight of these 36 words were composed of two parts, which made them significantly longer than the rest of the words. Further on, after testing this task in our third study, we decided to remove the longer stimuli, for a possibly better sensitivity of the task.

In our last study, we have finally used 14 side effects related word stimuli for the assessment task and another 14 for the attentional retraining task. We have added the ABM task to a standard CBT relaxation protocol and we have named this new CBT protocol as ABM enhanced CBT relaxation intervention. Although we have not found significant evidence for the superiority of this new protocol, as opposed to the standard one, it showed a similar efficacy in reducing side effects of treatment and distress. As it was a one session intervention, we cannot draw firm conclusions on its efficacy, leaving thus an inquiry to be addressed by future research.

4.3. Practical contributions

One of our major objectives was to integrate an ABM intervention in a standard CBT protocol designed for the management of side effects of treatment in breast cancer patients. More specifically we compared an ABM enhanced CBT protocol with the standard CBT protocol alone

(i.e., relaxation plus guided imagery and specific suggestions for reduced chemotherapy side-effects), analyzing separately the effects of these two interventions on (1) side effects of chemotherapy and distress, as well as their effect on (2) response expectancies and attentional bias. Although our results are mainly negative, the development and implementation of these two protocols have important clinical implications.

First, to our knowledge this is the first attempt to use a computerized psychological assessment and intervention task with breast cancer patients. The general development of the study showed that all the women we enrolled were open to this type of procedures. Second, we have introduced our both protocols in a very difficult environment – the scheduled chemotherapy session at a busy oncological Institute – and we have managed to implement them successfully, against the odds. This was possible only with the support of the medical team, fact that highlights again the importance of a close interdisciplinary collaboration. The procedure that we have built can be used further in any of the ambulatory clinics in which chemotherapy session are being undertaken.

4.4. Limitations and future directions

Our research has its inherent limitations. We have discussed them specifically in the Discussion section of every study. Also, some general limitations need to be mentioned here.

First, one major limit of our research is law statistical power. This might have prevented us from finding significant relations between attentional bias and other variables of interest.

Second, we did not address the issue of the non-engaging attentional bias assessment and intervention task. As our research was mainly exploratory, in what concerns attentional bias towards side effects of chemotherapy, we decided to use the known standard assessment and training tasks, specific to the attentional bias domain. This kept us from considering the development of new, more engaging computerized tasks.

Third, again mainly due to its exploratory nature, our intervention protocol had only one session. Also, because the majority of our patients were based outside Cluj-Napoca, we could not expand the protocol to weekly sessions.

Forth, we only used self-report measures in order to assess distress and side effects of treatment. Future research should consider other complementary measures (e.g., physiological, behavioral, clinician-rated) in order to reach stronger conclusions.

Despite these inherent limitations, we believe that the present research has expanded the domain of attentional bias research in cancer patients, by focusing on attentional bias towards side effects of treatment in breast cancer patients. However, our results did not indicate a significant relation between attentional bias and response expectancies or other cognitive mechanism considered in the CBT framework, nor did they sustain a superiority of the new ABM enhanced CBT protocol. Still, they raised several interesting research questions. We described in the Discussion section, for specific studies, possible explanations of our findings that could inform future research. We hope that this research will stimulate further investigation of psychological mechanisms that might improve cognitive behavioral interventions for cancer patients.

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