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PAPER

Improving anxiety regulation in patients with breast cancer at the beginning of the survivorship period: a randomized clinical trial comparing the benefits of single-component and multiple-component group interventions

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Abstract

Objective   To compare in a multicenter randomized controlled trial the benefits in terms of anxiety regulation of a 15-session single-component group intervention (SGI) based on support with those of a 15-session multiple-component structured manualized group intervention (MGI) combining support with cognitive-behavioral and hypnosis components.

Methods   Patients with nonmetastatic breast cancer were randomly assigned at the beginning of the survivorship period to the SGI (n = 83) or MGI (n = 87). Anxiety regulation was assessed, before and after group interventions, through an anxiety regulation task designed to assess their ability to regulate anxiety psychologically (anxiety levels) and physiologically (heart rates). Questionnaires were used to assess psychological distress, everyday anxiety regulation, and fear of recurrence. Group allocation was computer generated and concealed till baseline completion.

Results   Compared with patients in the SGI group (n = 77), patients attending the MGI group (n = 82) showed significantly reduced anxiety after a self-relaxation exercise (P = .006) and after exposure to anxiety triggers (P = .013) and reduced heart rates at different time points throughout the task (P = .001 to P = .047). The MGI participants also reported better everyday anxiety regulation (P = .005), greater use of fear of recurrence–related coping strategies (P = .022), and greater reduction in fear of recurrence–related psychological distress (P = .017) compared with the SGI group.

Conclusions   This study shows that an MGI combining support with cognitive-behavioral techniques and hypnosis is more effective than an SGI based only on support in improving anxiety regulation in patients with breast cancer.

KEYWORDS
anxiety, cancer, distress, fear of recurrence, group intervention, oncology

1 | BACKGROUND

The beginning of the survivorship period is challenging for patients with breast cancer.[1] The persistence of short- and long-term consequences of cancer diagnosis and treatment during this period may cause anxiety.[2] Anxiety is an adaptive state[3] that may have detrimental effects on patients' physical (eg, amplification of physical symptoms such as pain and fatigue[4]) and psychological (eg, adaptation or anxiety disorder[4,5]) status when anxiety symptoms become excessive. Anxiety may also contribute to the development or maintenance of fear of recurrence,[6] the most frequently reported

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difficulty[7] and most prevalent unmet need of patients after cancer treatment.[8,9] Anxiety and fear of recurrence have been shown to remain stable over time[10,11] and not easy to regulate. Nevertheless, few psychological interventions have focused on this period[12,13] and no intervention has specifically addressed anxiety regulation.[14,15]

Meta-analyses on interventions targeting anxiety in breast cancer patients at various times in the disease trajectory have highlighted that tested interventions presented moderate effect sizes and suggested the need to combine components.[16] Finally, very few studies have addressed fear of recurrence[17] and there is still a gap in the literature about the optimal components to include in interventions addressing this fear.[17]

The objective of this randomized study was thus to compare the benefits in terms of anxiety regulation (measured both psychologically and physically) of a 15-session single-component group intervention (SGI) based on support with those of a 15-session multiple-component group intervention (MGI) combining support with cognitive-behavioral and hypnosis components. The cognitive-behavioral components were chosen because interventions using such components have shown larger effect sizes than interventions using other components on the treatment of anxiety-related conditions.[18–20] The hypnosis component was chosen because studies have shown that self-hypnosis training may be a rapid, cost-effective, and safe alternative to medication.[21] Moreover, a meta-analysis showed that adding hypnosis to cognitive-behavioral components enhances effect sizes of interventions.[22] The 15-session format was chosen based on Andersen's publication[23] as we expected that the practice of hypnosis would lead to changes in patients' relaxation response observable through changes in heart rate levels.

First, we hypothesized that the MGI would be more effective than the SGI in improving anxiety regulation ability both psychologically (anxiety levels) and physiologically (heart rates) and in diminishing psychological distress. Second, we hypothesized that the MGI would be more effective in improving anxiety regulation in everyday life, in reducing fear of recurrence and functioning impairments associated with this fear, and in increasing the use of fear of recurrence–related coping strategies and in improving patients' mental adjustment to cancer. Third, we hypothesized that patients in the MGI would report greater benefits of intervention participation.

2 | METHODS

2.1 | Subjects and setting

This multicenter randomized controlled trial was conducted in Belgium. The local ethics committees approved the study. Women diagnosed with nonmetastatic breast cancer who had been surgically treated were approached during radiotherapy or 1 month after intraoperative radiotherapy. Exclusion criteria were age <18 years, nonfluency in French, severe cognitive impairment, severe and/or acute psychiatric disorder, and completion of treatment >1 year previously. Written informed consent was obtained from all participants.

2.2 | Study design

Participants completed a first assessment with an independent investigator (T1) just before study entry and were then randomly assigned to SGI or MGI on a 1:1 basis within cohorts of 12 women. Computer-generated group allocation was done inside each institution and concealed till baseline completion. A second assessment (T2) occurred immediately after intervention completion.

2.3 | Group interventions

Both interventions were delivered in a closed-group format (in groups of 6 participants) and comprised 15 weekly 120-minute sessions occurring within a 6-month period. Similarities and differences between both interventions are described in Table S1.

The SGI consisted of an enhanced standard care based on support (from peers and the group therapist) and on experience sharing. Seven clinical psychologists conducted the SGIs.

The MGI combined support with cognitive-behavioral and hypnosis components. The cognitive-behavioral components focused on expanding coping strategies, developing problem-solving skills, optimizing communication with caregivers and health professionals, and promoting the use of personal and social resources. Cognitive restructuring was used to address irrational thoughts. Sessions were structured around 3 themes: treatment side effects, fear of recurrence, and social support. Anxiety regulation was addressed throughout the sessions. Hypnosis was taught to patients as a strategy promoting anxiety regulation. Two clinical psychologists conducted the MGIs.

To achieve reliability, clinical psychologists followed a session-by-session structured manual. So that reliability is further ensured, regular intervisions between clinical psychologists and the study coordinators were organized. Audio and video recordings of all sessions were collected to be used in these intervisions if needed. Clinical psychologists conducted only 1 type of interventions to avoid contamination. Basic skills acquired by psychologists during their university training were sufficient for the SGI while a specific training in hypnosis and cognitive-behavioral techniques was necessary for the MGI. All the psychologists had at least 1 year of experience in cancer care.

2.4 | Assessments

2.4.1 | Primary outcomes

2.4.1.1 | Anxiety regulation task

Patients' anxiety regulation was measured psychologically (state anxiety levels) and physiologically (heart rates) using a dynamic task. This task involved 2 subtasks: (1) 4-minute exposure to anxiety triggers through completion of the Mental Adjustment to Cancer Scale,[24] followed by a 12-minute self-relaxation exercise in which patients were asked to relax by using their own strategies; and (2) 4-minute exposure to anxiety triggers through completion of the Fear of Cancer Recurrence Inventory,[25] followed by a 12-minute guided hypnosis exercise in which patients were asked to listen to an audio recording

of a hypnotic induction script. The subtasks were separated by a period of questionnaire completion.

State anxiety levels. Patients were asked to report their state anxiety just after both exposures to anxiety triggers and regulation exercises using a 10-cm visual analog scale (VAS; with the extreme left defined as "not at all anxious" and the extreme right defined as "extremely anxious"). The VAS was used because such scales have been shown to be appropriate and adequate for the assessment of emotional states.[26,27]

Heart rate measurement. Heart rate (in beats per minute) was measured throughout the assessment procedure using an ambulatory digital Holter recorder (Lifecard CF, Temec Instruments and Be. Med Sprl).

Relaxation Strategies Questionnaire. This self-report questionnaire, developed for this study, asked patients to report which of the 11 relaxation strategies (yes/no) they had used during the self-relaxation exercise (eg, muscular relaxation, breathing exercise, and self-hypnosis) and whether they used those strategies in their everyday life.

2.4.1.2 | Psychological distress

Hospital Anxiety and Depression Scale. The Hospital Anxiety and Depression Scale (HADS)[28] is a 14-item 4-point self-report instrument (Table 1). The use of the total score is recommended to assess psychological distress.[29]

2.4.2 | Secondary outcomes

2.4.2.1 | Everyday anxiety regulation

Patients were asked to report the level of anxiety felt in their everyday lives on a 10-cm VAS, with the extreme left defined as "never anxious" and the extreme right defined as "always anxious."

2.4.2.2 | Fear of Cancer Recurrence Inventory

The Fear of Cancer Recurrence Inventory (FCRI) is a 47-item 5-point self-report scale[25] (Table 1). The total score was not used in this study because we hypothesized that contrary to the other subscales, the coping strategies subscale score would increase at T2.

2.4.2.3 | Mental Adjustment to Cancer scale

The Mental Adjustment to Cancer (MAC) scale is a 40-item 4-point self-report measure of 5 psychological dimensions of mental adjustment in patients with cancer[24,30] (Table 1).

2.4.2.4 | Patients' Perception of Group- and Intervention-Related Benefits Questionnaire

Patients completed this questionnaire specially developed for this study at the end of T2. The group-related benefits section (adapted from Andersen[31]) assessed respondents' perceived involvement in (1 item) and receipt of support from the group (1 item). Patients rated each item using a 10-point Likert scale ranging from "not at all" (1) to

"extremely" (10). Intervention-related benefits were assessed using 5 dimensions (Table 2). Responses were structured by a 5-point Likert scale ranging from "not at all" (1) to "very much" (5). Cronbach α values for these dimensions were 0.80, 0.95, 0.93, 0.87, and 0.91, respectively.

2.5 | Statistical analyses

Sample size calculation was done based on an expected difference on the HADS scores between T1 (end of treatment) and T2 (6 months after the end of treatment) of 5 points for MGI and 1 point for SGI. This difference of HADS scores was chosen "a priori" as there were no available data on the other primary outcomes to use for sample size calculation. So that this difference can be demonstrated with an α of 0.05 and a power of 0.80, 130 complete cases per arm were needed. Interim analyses were done before the expected sample size (260 patients) was reached. These interim analyses were performed for the following reasons: (1) a slower than expected recruitment of patients and (2) the end of the funding. As differences in changes in HADS total scores between groups were lower than expected, the study was stopped.

Baseline characteristics of patients in the 2 study arms were compared using parametric and nonparametric tests (Student t test, χ^2 test, and Mann-Whitney test), as appropriate. Benefits of group interventions were assessed using group-by-time multivariate analysis of variance (MANOVA) or the Mann-Whitney U test. Data were analyzed according to intention-to-treat and completer case analyses. The method last observation carried forward (LVCF) was used for imputing missing data. The LVCF approach has been chosen as missing values were not at random. Under the missing-not-at-random assumption, a robust model of the dropout process would have been needed to use multiple imputation methods.[32] Not enough data were available to construct such a model. We therefore used the LVCF approach. State anxiety VAS scores and heart rates obtained at T1 and T2 in each group were compared using the Wilcoxon matched-pairs test. Heart rate analyses controlled for potential confounding variables (medications; body mass index; nicotine, alcohol, caffeine, and theine consumption in the 24 h before the assessment; and number of hours of physical activity and sleep in the 24 h before the assessment). Cohen d effect sizes were calculated based on comparing the SGI and MGI in terms of the differences in scores between T1 and T2. All tests were 2-tailed, and the α was set to 0.05. Analyses were performed using the IBM SPSS Statistics software for Windows (version 22.0; IBM Corp, Armonk, New York).

3 | RESULTS

3.1 | Subjects

Patient recruitment was from December 2010 until June 2013. Of 884 consecutive eligible patients approached, 177 (20%) agreed to participate in the interventions (Figure 1). Data from 159 patients (28 cohorts) were analyzed. Characteristics of patients who dropped out or missed the T2 assessment did not significantly differ from those of participating patients except for their cultural origin; those

TABLE 1 Comparison of intervention benefits

| | SGI (n = 77) | | | | MGI (n = 82) | | | | MANOVA | | | |
| | Before Intervention | | After Intervention | | Before Intervention | | After Intervention | | Time | | Group by Time | |
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	$F_{1,157}$	P	$F_{1,157}$	P
Anxiety regulation task[a]												
First subtask												
State anxiety level after triggers	2.8	2.9	2.6	2.9	2.4	2.7	2.0	2.3	1.49	.224	0.25	.619
State anxiety level after self-relaxation	1.8	2.2	2.2	2.7	2.0	2.6	1.5	2.2	0.13	.723	7.64	.006
Second subtask												
State anxiety level after triggers	2.6	2.6	2.6	2.5	3.1	3.0	2.0	2.4	8.70	.004	6.29	.013
State anxiety level after guided hypnosis	1.6	2.4	1.4	1.9	1.8	2.7	1.2	2.0	4.44	.037	0.92	.338
Hospital Anxiety and Depression Scale												
Anxiety	8.3	4.5	7.3	4.5	8.7	4.5	7.6	4.3	16.04	<.001	0.07	.785
Depression	4.6	3.7	4.1	3.6	5.0	4.4	3.8	3.8	11.10	.001	2.63	.107
Distress	12.8	7.3	11.4	7.2	13.8	7.8	11.3	7.3	19.42	<.001	1.26	.263
Everyday anxiety regulation[a]												
Anxiety level	4.4	2.6	4.3	2.6	5.3	2.8	4.0	2.6	12.42	.001	8.12	.005
Fear of Cancer Recurrence Inventory[b]												
Triggers	15.3	6.8	15.6	7.6	15.3	7.2	15.1	7.6	0.01	.920	0.30	.582
Severity	17.3	6.7	15.6	7.3	18.0	6.4	15.7	7.5	28.25	<.001	0.74	.392
Psychological distress	6.2	4.3	6.1	4.5	7.7	4.5	6.1	4.5	9.65	.002	5.81	.017
Coping strategies	20.5	8.5	19.2	8.8	22.8	7.9	24.2	7.6	0.01	.918	5.32	.022
Functioning impairments	5.1	5.5	4.1	6.1	5.5	6.4	4.4	5.7	10.23	.002	0.01	.913
Insight	1.7	2.9	1.3	2.5	1.7	2.2	1.6	2.3	3.01	.085	0.66	.419
Reassurance	1.9	2.4	2.1	2.8	2.1	2.5	2.3	2.6	0.96	.327	0.01	.905
Mental Adjustment to Cancer Scale												
Fighting spirit	51.3	6.0	50.9	5.5	51.8	5.7	52.1	5.5	<0.01	.994	0.87	.353
Anxious preoccupation	23.5	4.4	21.9	4.4	23.7	3.9	22.8	4.4	20.82	<.001	1.18	.279
Helplessness/hopelessness	9.1	3.0	9.0	3.2	9.6	3.8	8.9	3.2	4.06	.046	2.29	.132
Fatalism	17.6	3.6	18.2	3.8	18.2	4.1	17.7	3.9	<0.01	.970	3.70	.056
Avoidance	1.8	1.1	1.8	1.1	1.8	1.1	1.8	1.0	0.10	.758	0.42	.517

Abbreviations: MANOVA, multivariate analysis of variance; MGI, multiple-component group intervention; SD, standard deviation; SGI, single-component group intervention.

[a]Measured with visual analog scales.

[b]Missing data for 1 patient.

TABLE 2 Patients' perceptions of group- and intervention-related benefits

| | | SGI (n = 52) | | MGI (n = 73) | | |
	No. of items	Mean	SD	Mean	SD	P^a
Group-related benefits						
Involvement in the group	1	6.6	2.7	8.2	2.1	<.001
Support by the group	1	6.2	3.0	8.4	1.9	<.001
Intervention-related benefits						
Side effects management	4	2.0	1.0	3.1	0.9	<.001
Anxiety regulation	7	2.1	1.1	3.5	0.9	<.001
Positive reappraisal	5	2.5	1.3	3.7	0.8	<.001
Acceptance and personal growth	6	2.5	1.2	3.4	0.9	<.001
Interpersonal skills	5	2.7	1.2	3.5	0.8	<.001

Abbreviations: MGI, multiple-component group intervention; SD, standard deviation; SGI, single-component group intervention.

[a]Mann-Whitney U test; 5 patients (4 patients in the SGI and 1 patient in the MGI) did not participate in the interventions and thus did not complete the questionnaire.
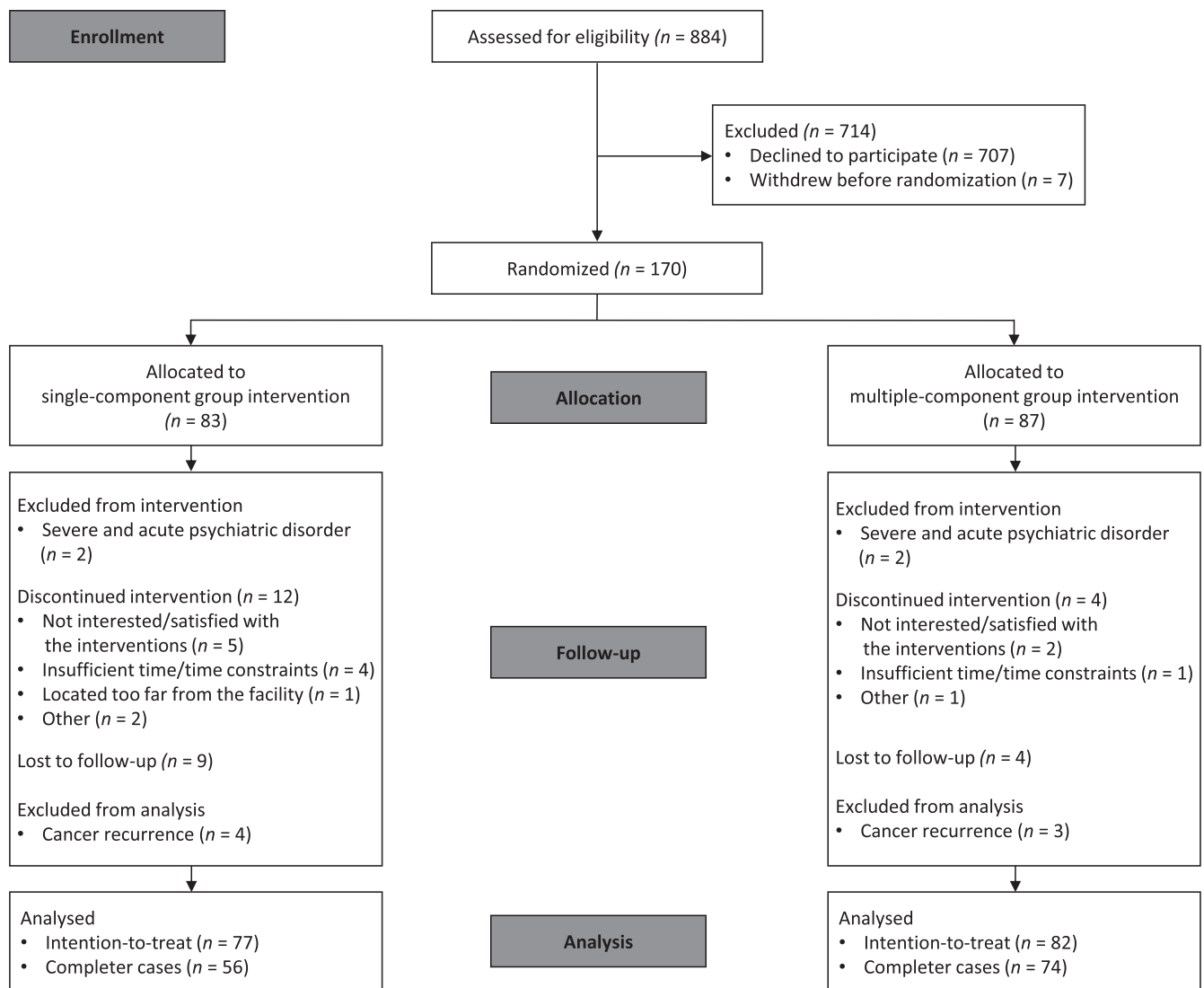
FIGURE 1 Flow diagram of study participants

who dropped out or missed the T2 assessment (both in the MGI and in the SGI) were more frequently from regions other than Western Europe ($P = .009$). For the heart rate analyses, 42 patients were excluded because they were taking medications that can affect cardiovascular responses and data were missing for 17 patients owing to recording problems.

3.2 | Sociodemographic, disease, and treatment characteristics

Patients in the sample ranged in age from 30 to 82 years old, with an average age of 50.6 (SD = 10.1) years; 44% were married or cohabiting, 66% had at least high school education, and 17% worked part or full time. Five percent of these patients were diagnosed with carcinoma in situ, 79% had stage I or II, 14% had stage III, and for 2% the stage was unknown. Sixty-nine percent of patients underwent a lumpectomy, and 31% underwent a mastectomy. Thirty-one percent of patients had received neoadjuvant chemotherapy, and 39% had received adjuvant chemotherapy. Hormonotherapy was scheduled for 76% of patients, and 17% of patients had received biological

therapy (trastuzumab). Patients enrolled in the study an average of 4.0 months following radiotherapy (SD = 4.2). The majority of patients (80%) were from Western Europe. Analyses revealed no significant difference between study arms at baseline, with the exception that a greater number of patients treated by hormonotherapy were assigned to the MGI ($P = .029$; 84% versus 69%). No significant difference was observed in psychotropic medication use or psychological and psychiatric support initiated after cancer diagnosis or during intervention participation.

3.3 | Primary outcomes

In the anxiety regulation task, group-by-time MANOVA showed significantly reduced MGI participants' state anxiety levels after the self-relaxation exercise ($P = .006$, Cohen $d = 0.44$) and after the second exposure to anxiety triggers ($P = .013$, Cohen $d = 0.40$) compared with SGI participants (Table 1). Similar results were observed for the Wilcoxon matched-pairs tests ($P = .008$ after the self-relaxation exercise; $P < .001$ after the second exposure to anxiety triggers). Multivariate analysis of variance revealed no group-by-time change for

heart rate. Wilcoxon matched-pairs tests revealed significantly reduced MGI participants' heart rates at different times throughout the task ($P < .001$ to $P = .047$), compared with SGI participants (Figure 2).

Regarding psychological distress, MANOVA analyses revealed no group-by-time change in patients' anxiety, depression, and distress levels but a time effect was observed (HADS: $P < .001$ to $P = .001$).

Strategies used during the self-relaxation exercise did not differ between groups at T1 but differed significantly at T2 ($P < .001$); 64% ($n = 47$) of patients in the MGI group and 9% ($n = 5$) of those in the SGI group reported using self-hypnosis at this time. No difference between groups in hypnosis or self-hypnosis practice was observed at T1, whereas 60% ($n = 49$) of patients in the MGI group and 7% ($n = 5$) of those in the SGI group reported using these practices at T2 ($P < .001$).

3.4 | Secondary outcomes

Group-by-time MANOVA showed that compared with patients attending the SGI, those attending the MGI showed better everyday

anxiety regulation ($P = .005$, Cohen $d = 0.45$), significantly greater use of fear of recurrence–related coping strategies (FCRI: $P = .022$, Cohen $d = 0.37$), and greater reduction in fear of recurrence–related psychological distress (FCRI: $P = .017$, Cohen $d = 0.38$; Table 2).

Intervention attendance differed between groups, with patients in the MGI attending an average of 10.2 (SD, 4.1) and those in the SGI attending an average of 5.6 (SD, 4.3) of the 15 group sessions ($P < .001$). Patients in the MGI group reported greater perceived group- and intervention-related benefits than did those in the SGI group (all $P < .001$; Cohen d, 0.84-1.84; Table 2). Completer case analyses yield similar results than those of the intention-to-treat analyses in terms of statistically significant effects even though P values were slightly different.

4 | CONCLUSIONS

First, as regards primary outcomes, the results of this study were mixed. As regards anxiety regulation, the results of this study showed
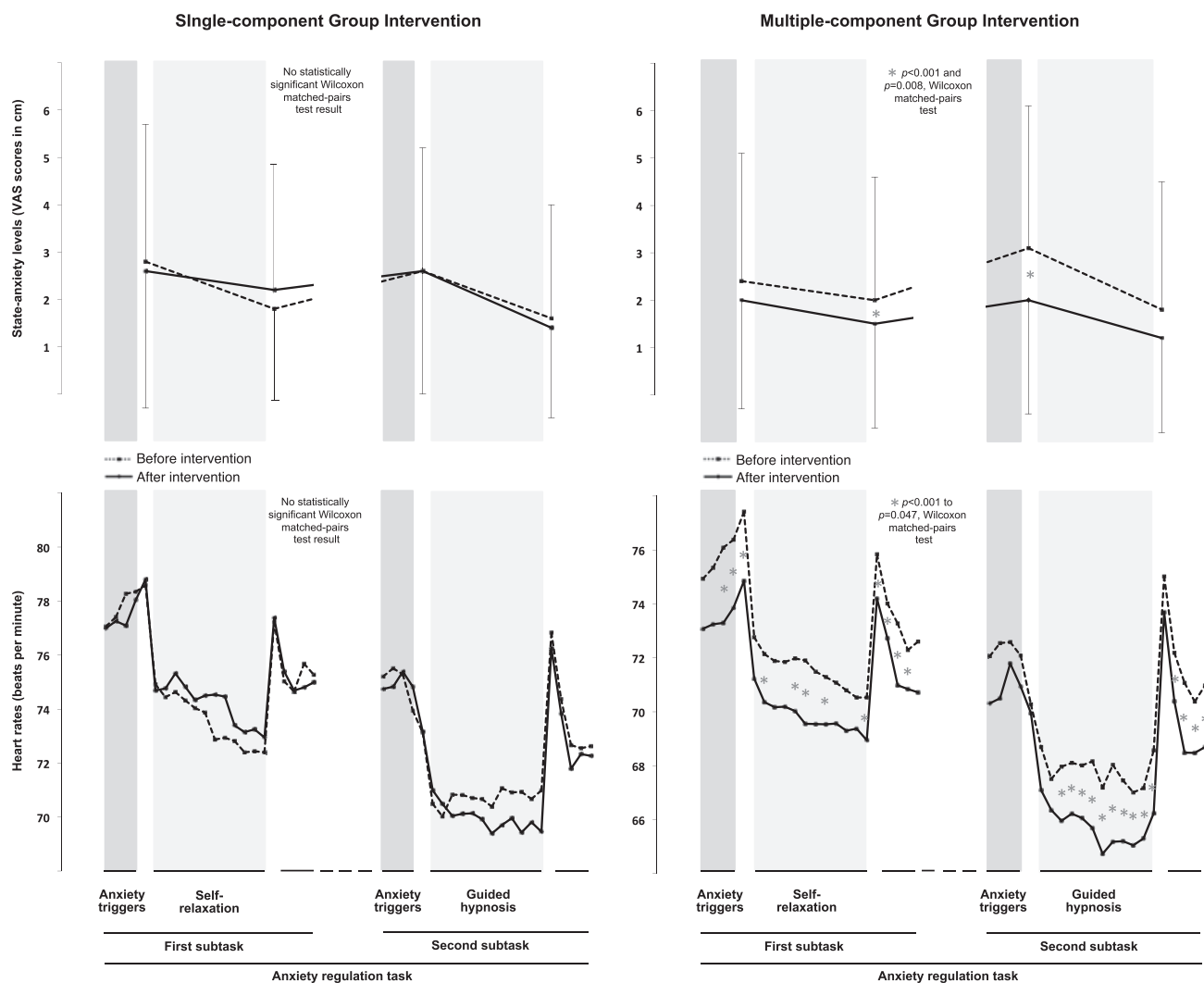

FIGURE 2 Anxiety regulation task. Comparison of state anxiety levels (state anxiety VAS score) and heart rates (beats per minute) before and after the interventions. Multivariate analysis of variance showed significant group-by-time effects on state anxiety after the self-relaxation exercise ($P = .006$) and after the second exposure to anxiety triggers ($P = .013$). No multivariate analysis of variance group-by-time changes were observed in terms of heart rates. Abbreviation: VAS, visual analog scale

the added benefits of the MGI compared with the SGI in improving anxiety regulation during the anxiety regulation task. This improvement was observed at the psychological and physiological levels. The greater efficacy of the MGI compared with that of the SGI in improving patients' ability to elicit a relaxation response[33] may be explained by the fact that the MGI, beyond support, addresses triggers of anxiety, helps patients find concrete strategies to implement in their everyday lives, and motivates patients to use new anxiety regulation behaviors. It should be underlined here that 60% of patients in the MGI reported practicing hypnosis or self-hypnosis exercises at home. As regards psychological distress, results show that there was no added benefit of the MGI compared with the SGI in terms of decrease in anxiety, depression, and distress levels. Anxiety, depression, and distress diminished in both groups over time.

Second, as regards secondary outcomes, the results of this study were also mixed. They revealed the greater efficacy of the MGI in improving anxiety regulation in everyday life and in reducing fear of recurrence–related psychological distress. They showed also that patients in the MGI increased their use of fear of recurrence–related coping strategies. Both group interventions were, however, equally effective in reducing the severity of fear of recurrence and functioning impairments associated with this fear and in improving mental adjustment to cancer. It should be underlined here that patients' level of fear of recurrence was, on average, above the clinically relevant cutoff point[34] and remained high after both interventions. The lack of difference between group interventions in reducing the severity of patients' fear and functioning impairments associated with this fear may be explained by the fact that only 4 of the 15 sessions addressed fear of recurrence specifically.

Third, patients perceived these added benefits, considering the MGI to be more helpful than the SGI. The substantial difference in attendance rates, dropout rates, and missed T2 assessment in favor of the MGI group could be explained by the MGI thematic focus and hypnosis component. The MGI thematic focus on treatment side effects, fear of recurrence, and social support allowed to tackle these issues thoroughly. As several sessions were conducted around a theme, this allowed patients who missed some sessions to still benefit later from the intervention and may have prevented them from dropping out. The hypnosis component could also explain the higher attendance rates as participants were discovering a new way to regulate their anxiety. The higher attendance rates could also be explained by the fact that participants were contacted by phone prior to each session. Finally, the fact that MGI patients attended on average 10 out of the 15 sessions scheduled may indicate that fewer sessions could also be appropriate.

This study has several strengths. First, the study compared 2 group interventions with different components that have been demonstrated as efficient in previous studies. Second, to our knowledge, this study is the first to assess anxiety regulation with a dynamic task. This unique method of assessment has many advantages: this is a nonstatic assessment, with a greater sensitivity to change, reflecting more accurately patients' ability to use regulation strategies when they experience anxiety.

This study has some limitations. First, clustering at the hospital level and at the group level could have had an impact on the power of

the study. Second, heart rate assessment was used to assess patients' relaxation response at a physiological level, but it should be underlined that a number of patients could not be assessed because of medication factors. Such an assessment remains useful as it allows an in-depth study of the relaxation response and of its physiological impact.

In terms of recruitment, it should be underlined that only a minority (20%) of the eligible participants agreed to participate. This rate corresponds to the percentage of women desiring psychological support in psychooncology as reported previously[35] and may also be explained by the relatively broad sources of psychological support available for cancer patients in Belgium, allowing patients to have a varied choice of interventions.

In conclusion, our results indicate that an MGI combining support with cognitive-behavioral therapy and hypnosis is clinically useful in helping patients with breast cancer better regulate their anxiety both psychologically and physiologically at the start of the survivorship period. Our study targeted a wide range of difficulties that patients face at that time. The high levels of fear of recurrence found in the participants confirm the need to design specific interventions for patients at the start of the survivorship period and to target more specifically anxiety regulation and fear of recurrence. Further studies are still needed to increase the effect sizes of interventions. Interventions focusing on anxiety regulation and fear of recurrence should certainly include components targeting more specifically both emotion regulation and the contents and process of fear.

TRIAL REGISTRATION

ClinicalTrials.gov identifier NCT01797354.

CONFLICT OF INTEREST

There are no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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