

Psychological Optimization of Expectations to Prevent Nocebo Side Effects in Breast Cancer – 2 Case Reports

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Keywords

Breast cancer · Psychological interventions · Psycho-oncology · Nocebo effect · Prevention · Side effects · Expectations

Summary

Background: Expectations can influence treatment outcomes in a positive and negative way (placebo and nocebo effects). These 2 case reports describe a cognitive-behavioral ‘side effect prevention training’ (SEPT) for breast cancer patients at the start of endocrine therapy. The training focuses on the optimization of patients’ treatment expectations to reduce patients’ side effect burden and enhance their quality of life during medication intake. **Case reports:** Two patients are presented, who attended the prevention training as part of a randomized controlled study. The intervention consisting of psychoeducation about nocebo effects, activation of resources, and side effect management to enhance self-efficacy was analyzed quantitatively and qualitatively. Treatment expectations before and after the intervention were evaluated. Side effects and quality of life were measured before, 3, and 6 months after the start of endocrine treatment. Both patients reported that they have benefited from the training. Different interventions have been revealed to be most important. Both patients showed improved treatment expectations, reduced side effects, and increased quality of life. **Conclusion:** In both cases, psychological support in handling feared side effects seemed to be suitable to reduce harm induced by cancer treatment. Modifying treatment expectations could be a worthwhile contribution in enhancing the health care of breast cancer patients.

Schlüsselwörter

Brustkrebs · Psychologische Interventionen · Psychoonkologie · Nocebo-Effekt · Prävention · Nebenwirkungen · Erwartungen

Zusammenfassung

Hintergrund: Erwartungen können den tatsächlichen Verlauf einer medizinischen Behandlung beeinflussen – im positiven wie im negativen Sinne (Placebo- bzw. Nocebo-Effekt). Anhand zweier Fallberichte wird eine psychologische Kurzzeitintervention vorgestellt, die für Brustkrebspatientinnen zu Beginn der Antihormontherapie konzipiert wurde («Antihormonelle Therapie erfolgreich meistern», ATEM). Den inhaltlichen Schwerpunkt bildet die Optimierung individueller behandlungsrelevanter Erwartungen mit dem Ziel, die Belastung durch Nebenwirkungen während der Medikamenteneinnahme zu verringern und die Lebensqualität zu verbessern. **Falldarstellungen:** Zwei Patientinnen, die im Rahmen einer randomisierten kontrollierten Studie am ATEM-Präventionsprogramm teilnahmen, werden vorgestellt. Die Kurzzeitintervention, die eine patientenzentrierte Aufklärung zu Nocebo-Effekten, Ressourcenaktivierung und Stärkung der Selbstwirksamkeitserwartungen im Umgang mit individuell befürchteten Symptomen umfasst, wurde qualitativ und quantitativ ausgewertet. Erhoben wurden die Behandlungserwartungen vor und nach der Intervention sowie die tatsächliche Nebenwirkungsbelastung und Lebensqualität vor Beginn der Antihormontherapie und im Follow-up nach 3 und 6 Monaten. Beide Patientinnen berichteten, von dem Programm profitiert zu haben, wobei sich unterschiedliche Schlüsselinterventionen zeigten. Bei beiden Patientinnen verbesserten sich die behandlungsrelevanten Erwartungen, verringerte sich die Nebenwirkungsbelastung und steigerte sich die Lebensqualität. **Schlussfolgerung:** Die psychologische Unterstützung zum Umgang mit befürchteten Nebenwirkungen erwies sich in beiden Fällen als geeignet, um die Belastung durch Krebsbehandlungen zu reduzieren. Die Optimierung von Behandlungserwartungen könnte einen wertvollen Beitrag zur Verbesserung der Versorgung von Patientinnen mit Brustkrebs leisten.

Background

One out of every 8 women in Germany gets breast cancer during her lifetime [Robert Koch-Institut, 2013]. In patients with hormone-dependent breast cancer, relapse-free survival can be significantly enhanced by a 5- to 10-year course of endocrine therapy [Davies et al., 2013]. Still, half of the patients cancel the treatment prematurely [Partridge et al., 2003], mainly because of the bothersome side effects and a limited quality of life [Cella and Fallowfield, 2008]. Side effects are defined as unintended effects of medications [Barsky et al., 2002]. They can be either positive and beneficial or negative and harmful. In what follows, however, we apply the term only to negative, undesired side effects. Interventions for the reduction and management of side effects appear to be necessary to reduce the high drop-out rates and to improve the quality of life.

Nocebo Effects

Side effects can be triggered not only by the pharmacodynamics of a drug, but also by nocebo effects. Nocebo effects (from the Latin, nocebo: 'I will harm') refer to side effects that occur even though placebos are taken instead of active pharmaceuticals [Faasse and Petrie, 2013]. Nocebo-induced side effects have been seen in clinical trials of the treatment of various medical illnesses [Enck et al., 2013]. For cancer treatment, it is highly important that nocebo-induced side effects also occur when the actual drugs are taken [Garg, 2011]. The nocebo effect is notably expressed by unspecific symptoms (i.e., symptoms that are not attributable to the pharmacological effects of a drug) [Nestoriuc et al., 2010; Barsky et al., 2002]. However, the nocebo effect can also heighten specific side effects (symptoms that are the result of pharmacodynamics) or lead to their initial occurrence. This can be seen from review articles that show corresponding side effect profiles of the placebo arms of clinical trials and the use of active pharmaceuticals [Shedden-Mora et al., 2011]. In patients with breast cancer who are treated with endocrine therapy, the side effect profile in the placebo group resembles those of the verum group [Whelan et al., 2005]. A typical nocebo effect in treating cancer is the greater incidence of nausea during chemotherapy if the patients expect more nausea [Sohl et al., 2009; Colagiuri and Zachariae, 2010]. Also with endocrine therapy, greater side effects occur if the patients expect them [Nestoriuc et al., 2011]. Thus it must be assumed that an appreciable share of the side effects of endocrine therapy can be explained by nocebo effects (nocebo-induced side effects). The causes are assumed to be side effect-related expectations, negative attitudes toward treatment and past experience [Bingel, 2014]. Other important components seem to be focusing one's attention on specific bodily events and the false attribution of previously existing symptoms to the drug [Barsky et al., 2002; Faasse and Petrie, 2013].

Self-Regulation Model

According to Leventhal's Common-Sense Model of Self-Regulation [Leventhal et al., 2003], a patient develops both cognitive and emotional representations of his illness and its treatment, and therefore also different coping strategies. Previous studies evaluat-

ing the Common-Sense Model in breast cancer patients show that expectations of being able to control one's physical health are correlated with coping behavior [Rozema et al., 2009] and also predict psychological stress [McCorry et al., 2013]. Thus it appears useful to raise coping expectations.

The SEPT Program

In light of the research here described, the authors designed a 'Side Effect Prevention Training' (SEPT), with the goal of positively influencing drug-related expectations and internal control beliefs (coping expectations) in patients who are beginning endocrine therapy, to reduce the occurrence of side effects during the course of medication and to improve the quality of life (table 1). SEPT includes significant interventions which have been discussed as helpful in the field of placebo and nocebo research [Colloca and Finniss, 2012; Enck et al., 2013; Bingel, 2014]. These include psychoeducation about the disease and the treatment, adapted to the patients' prior knowledge and wishes, a kind of individualized 'informed consent'; promotion of doctor-patient communication; awareness of the nocebo effect; use of learning mechanisms and conditioning processes by coupling the medication regime with sensory experiences (e.g., a beautiful song) and association of the administering of the medication with pleasant emotions and expectations, for example through imagination exercises. Training in techniques to reduce anxiety and depression can also be useful, because these feelings are probably related to nocebo effects. The techniques are also intended to improve expectations of self-efficacy in coping with side effects and also attention control. It is important to emphasize that preoccupation with one's expectations, in the sense of acquiring negative expectations about the treatment, does not seem to entail increased anticipatory anxiety [Colagiuri et al., 2013].

Previous cognitive behavioral approaches to the reduction and management of side effects in breast cancer treatment have been aimed at side effects that have already occurred [Duijts et al., 2012; Mann et al., 2012]. The main focus of these group programs has hitherto mainly been dealing with hot flashes. The programs include 6 units of 90 min each for relaxation training, sports and stress management. There are still no evaluated treatment approaches that work explicitly with the changing treatment expectations and are preventive in nature. SEPT is a brief individual preventive intervention of 3 sessions, which can be economically integrated into the clinical routine and in different contexts, such as psycho-oncology counseling, individual psychotherapy, or psychological care during a stay in rehab.

Since the recently released S3 guideline for psycho-oncology [Leitlinienprogramm Onkologie (Guidelines for Oncology), 2014] recommends as an expert consensus, to offer psychoeducation to all cancer patients, regardless of their degree of distress, participation should be allowed for all breast cancer patients who are beginning endocrine therapy, in a prevention and psychoeducational program such as SEPT.

Through two case studies, this article presents the psychological effort to modify expectations, with the goal of prevention of side effects from long-lasting courses of medication. One focus is on the

Table 1. Goals and content of the SEPT prevention program.

<p>Session 1: 'Endocrine therapy as protection and companion for the next few years.'</p> <p><i>Goals:</i> Optimization of expectations (regarding benefits and side effects of the treatment), positive integration of the medication regime into daily life.</p> <p><i>Content:</i> Psychoeducation a) on the operating principle of endocrine therapy; b) on the impact of expectations and nocebo effects; imagining a protective image.</p>
<p>Session 2: Dealing with possible side effects: 'I'm not going to let it get me down!'</p> <p><i>Goals:</i> Strengthening self-efficacy; reduction of fears.</p> <p><i>Content:</i> Psychoeducation about the relationship of thoughts, feelings and behavior; development of individual coping skills for dealing with side effects (creating a tool kit).</p>
<p>Session 3: 'I watch out for myself and I'm active!'</p> <p><i>Goals:</i> Attention control, resource activation; effective communication with doctors.</p> <p><i>Content:</i> Assembly of personal sources of strength; tips on doctor-patient communication.</p>
<p>3 refresher phone calls, 1, 3 and 6 months after the program: 'I am safe and am using my strategies!'</p> <p><i>Goals:</i> Support for carrying out the coping plan; promotion of current resources.</p>

patients' perspective and the qualitative and quantitative evaluations of treatment-related expectations, side-effect burden and quality of life. The feasibility of manual-based intervention is also examined, along with drawbacks of this approach.

Method

Design

The SEPT prevention program is currently being evaluated by Y.N. in a DFG-funded randomized controlled trial [von Blanckenburg, et al., 2013] at the university medical centers of Marburg and Hamburg-Eppendorf. The effects of the brief psychological intervention (SEPT) are being compared with those of a purely supportive therapy (ST), using the identical treatment setting and scope, as well as with medical treatment as usual (TAU). Following the CARE guidelines [Gagnier et al., 2013], 2 case reports are presented here of patients who participated in the SEPT program in Marburg. The interventions were conducted by P.v.B. and were under S.R.-S.'s psycho-oncological supervision. By way of illustration, 2 patients were selected who differ significantly in their demographic and medical background (menopausal status, stage of tumor, type of endocrine therapy) as well as their prior knowledge of the treatment and the disease and their attitudes about the endocrine therapy. Both patients gave informed consent to the case reports and agreed to the publication of the results. Before the intervention began, both patients received validated and standardized patient information about the endocrine therapy [Heisig et al., 2015]. The 'Mini-Dips' short diagnostic interview [Margraf, 1994] was conducted to make sure that the patients had no serious mental disorders, which would have required more intensive psychotherapeutic care than the 3-hour intervention.

Qualitative Evaluation

Video analysis and notes of the individual sessions, as well as copies of the edited intervention materials, were used for the qualitative descriptions and evaluations. Patient feedback about particular sections and interventions was briefly noted by the therapist, and the patients were also given questionnaires to fill out in an open response format.

Quantitative Evaluation

Data from standardized questionnaires were evaluated for the quantitative progression analyses. The side effects and symptoms at baseline as well as the quality of life were evaluated before the start of the endocrine therapy as well as at the follow-up 3 and 6 months after start of treatment. The incidence and intensity of 44 side effects (intensity 0 = none, 3 = severe) were measured with an extended version of the General Assessment of Side Effects (GASE) [Rief et al., 2011]. The questionnaire was expanded to include the symptoms that are typi-

cally described as side effects of endocrine therapy. Cumulative values were calculated for all symptoms. An assessment was also made of whether the side effect was because of the medication and how well the patient could cope with it (coping: 0 = poor, 3 = very good).

Quality of life was assessed using the scale for overall quality of life from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [Aaronson et al., 1993], using a 7-step Likert scale. Here, higher values mean better quality of life.

To measure the change in expectations of side effects and the expected coping with side effects, the GASE-Expect, a modified version of the GASE [Rief et al., 2011], was used before and after the SEPT program. This assessed whether and to what intensity the patients expected 44 different side effects (expected intensity: 0 = none, 3 = severe) and how they evaluated their coping options (expected coping: 0 = poor, 3 = very good). Cumulative values for expectations of side effects and average values for evaluation of coping were calculated for all symptoms.

Attitude toward endocrine therapy was captured by the item 'How would you rate the endocrine therapy overall, based on the information available so far?', using a 5-step response format (1 = negative, 5 = positive) at all 4 measurement points.

The longitudinal results were descriptively compared with the preliminary values of the control groups (ST, TAU).

Case Reports

Socio-demographic, Medical and Psychological Characteristics

Ms. Mohn (all names have been changed) was 49 years old at the time of the intervention, working part-time as a doctor (currently she is incapacitated by the cancer) and lived with her husband and two teenage children. She was premenopausal, suffering from Stage I breast cancer ($T_1N_0M_0$) and had had breast-preserving surgery with intraoperative irradiation, as well as 4 out of 28 radiation treatments, 4 weeks prior to the first session. She had no other physical diseases. The patient began the endocrine therapy (tamoxifen plus GnRH analogue) upon completion of SEPT. She described being psychologically stressed by the cancer diagnosis and the upcoming medical treatments. The Mini-Dips was normal. Ms. Mohn reported that because of her profession, she had considerable prior knowledge about endocrine therapy and an ambivalent attitude toward it. She said that she felt concerned about possible side effects.

Ms. Mey was 58 years old, worked full-time as a commercial employee (currently on sick leave), and lived with her husband. She was premenopausal, suffering from Stage II breast cancer ($T_1N_1M_0$) and had had breast-preserving surgery with intraoperative irradiation 6 weeks before the start of the intervention. She indicated that she has chronic hypertension. Before the first SEPT session, Ms. Mey had begun endocrine therapy (aromatase inhibitor) and had received

11 out of 28 radiation treatments. The Mini-Dips was normal. Ms. Mey reported that she is a tense person, and finds it difficult to relax. Since her cancer diagnosis, she has felt even more uneasy, with undefined anxiety.

Qualitative Case Report

We present here the most relevant information and the key interventions with regard to the modification of treatment expectations.

Ms. Mohn

Ms. Mohn stressed at the beginning of the program, that she is still not 100% sure whether she wants to undergo endocrine therapy. She said that she is afraid 'of aging very quickly and suddenly from artificially induced menopause' and does not 'see the drug Tamoxifen as only beneficial'. Her reason says, 'Yes, I'll take it! What choice do I have?', but she 'still does not feel that this is the right decision'. To clarify her ambivalence, the symbol of a scale was used to weigh the significance for the patient of the impact and side effects of endocrine therapy. It was important for Ms. Mohn that Tamoxifen should help 'to combat the tumor' and 'prevent metastases and recurrences'. On the scale of possible adverse effects, Ms. Mohn counted mood swings and dryness of mucous membranes. At this point, the patient weighted both sides of the scale as equally heavy ('It's balanced for me!'). Following the manual, the first session focused initially on the protective effect of endocrine therapy, while the fear of side effects was deliberately set aside. The aim was to encourage a new and more open attitude toward the drug. Ms. Mohn was encouraged to deliberately grapple with the decision of whether to use the drug, so as to make a decision about the treatment that seemed reasonable to her. She formulated her individual motivational sentence as follows: 'I take endocrine therapy because I want to be/stay healthy!' For deeper elaboration of this motivational clarification, the sentence was written on a postcard that Ms. Mohn had chosen from a collection. The postcard depicted a dancer, who for Ms. Mohn symbolized 'joie de vivre and vitality' and represented for her the motivation to proceed with the endocrine therapy.

Then an imaginative exercise was worked out, whereby Ms. Mohn developed an image of endocrine therapy that was personally useful for her. This was intended to help give Tamoxifen a positive image and to modify her treatment expectations with an individualized anchoring of the protective effect. Ms. Mohn's fantasy was that a guardian angel covers up the tumor and then sits on it, so that it becomes quite small, can no longer grow and eventually atrophies. The guardian angel symbolizes Tamoxifen for her. After these interventions, she stressed that it was important for her 'to give the drug a chance to work without thinking immediately about the side effects'. It was important to provide a reattribution on both the cognitive and emotional levels: from 'the pill as an enemy' which would cause bad side effects to 'the pill as a friend' with a protective function.

Furthermore, knowledge transfer about the nocebo effect occurred in the first session. There was a therapeutic conversation about the power of expectations and the danger of body scanning. Finally, Ms. Mohn came to the conclusion: 'I know there are many side effects, but I'm not going to get all of them. I'll listen to my body, but I will not look for side effects'.

At the beginning of the 2nd session, Ms. Mohn said that she had developed a more open attitude toward the drug ('I decided to at least give it a try!'). Then, individual problem-solving and behavioral plans were prepared to cope with the side effects that the patient feared most. The goal was to increase Ms. Mohn's self-efficacy expectations and lower her anxious expectations of side effects. Both mental and behavioral strategies were developed for dealing with mood swings, vaginal dryness/reduced libido and fatigue/lack of motivation (table 2). Ms. Mohn found this intervention especially relevant, making coping strategies concrete for her: 'Actually many strategies are already clear to me, but it is something else again to have them there in black and white – much more concrete!' She was motivated to put together a 'tool kit' with helpful content to make the strategies more tangible.

Ms. Mohn brought a cardboard box as a tool kit to the third session. This included items that would be helpful to the patient during her medication regime (e.g., an MP3-player with music, a favorite book) and index cards on which the coping strategies were written down.

A subsequent resource-oriented method for strengthening Ms. Mohn's resilience supplemented the specific problem-solving strategies for coping with

particular side effects. The deliberate attention to her personal resources was intended to help Ms. Mohn after surgery and during the adjuvant treatment to keep in mind the positive, rather than to focus on her physical symptoms. Ms. Mohn, among other things, regularly made time to spend with her husband, to take walks and to swim, as well as allowing for sufficient rest breaks. She made it clear that it would be very important for her in the future, to strike a balance between more beneficial activity and rest periods, and not to overextend herself ('I would like to slow down!').

Three refresher phone calls every few months are intended to assist the patient in carrying out the coping plan, to modify strategies and to promote current resources. Ms. Mohn had started taking the tablet and looked at this as a ritual part of each day. That makes taking the medicine an obvious thing to do, she said. She stored her endocrine tablets in a pill bottle with an angel on it. The sentence she worked out, 'Just slow down!', was very important for her and encouraged her to continue her self-care. She reported that she was experiencing hot flashes as a side effect of the endocrine therapy, but this did not interfere with her rest and she followed a strategy of always keeping a towel handy. She started also started doing Yoga and swimming, to reduce the hot flashes through adequate exercise. 'The only side effect that really bothers me is waking up at night and insomnia!' Ms. Mohn reported that it does help a little 'to have the tool kit next to the bed', but unfortunately the rules for sleep hygiene worked out during the refresher phone calls did not help. She concluded that she would probably have to just live with it.

Ms. Mohn concluded by assessing the SEPT program as very helpful. It particularly pleased her that she obtained 'so many specific strategies for dealing with side effects. That has given me a lot of strength'. (table 2)

Ms. Mey

Ms. Mey was under the impression that when she was hospitalized she was literally flooded with information that she was unable to absorb. Therefore, at the beginning of the program she was calmly given an explanation of how the aromatase inhibitor works. Ms. Mey reported that this knowledge gave her a greater sense of being in control ('I am a control freak!') and diminished somewhat her vague fear. Already before the program began, she said she was sure that she would take the endocrine therapy and indeed had already begun: 'This drug is my life insurance!' However she now understands better 'how it all works' and that gives her a 'good feeling'.

Ms. Mey described that at the moment she is not grappling with side effects ('I have no use for side effects'); however, she is concerned about possible weight gain. Currently Ms. Mey is particularly anxious about the uncontrollability of breast cancer ('Even with medication, you can never be sure that the cancer won't come back!'). She is currently very tense and takes out her frustration on those around her. Ms. Mey felt validated in her experience of anxiety. The uncontrollability of cancer is, understandably, an immense burden for many patients. Living with this fear, tolerating it and accepting it, is certainly one of the most difficult tasks for those affected [Waadt et al., 2011]. To modify Ms. Mey's self-efficacy expectations, we used a behavioral experiment to work out what influence thoughts and images could have on physical reactions and feelings. This was an individual image of relaxation, 'a blue sky in the mountains, with snow and absolute tranquility'. The patient was encouraged to spend a few minutes each day on the exercise. Another key intervention in the SEPT program is to figure out a personal protective image against endocrine therapy, since mental images for coping with the disease and strengthening one's coping expectations can be very important. The patient formulated it as follows: 'The endocrine therapy is for me like a huge black hammer, which strikes an anvil and thereby ensures that the cancer will not return. The pills are like a hammer for the cancer cells, which cleans things up'. She wanted to have this image in mind when taking the pills.

Ms. Mey described as 'very fascinating' the psychoeducation on the nocebo effect, which was conveyed at the end of the first session using patient stories. She said that it makes them realize the power their own thoughts can have on the emergence of feelings and side effects: 'The head plays a very great role!', was her conclusion.

At the beginning of Session 2, Ms. Mey reported that she had managed to take time for the relaxation image every day. This is doing her good, she said. She also thinks about the image of 'the hammer and anvil' when she takes her pills.

Table 2. Individual coping skills by Ms. Mohn and Ms. Mey to Deal with possible side effects of endocrine therapy

Tool kit	Mental strategies	Behavioral strategies
Ms. Mohn		
Mood swings	'I can do it, because I'm often strong', 'I will now do first what I find pleasant!', but also 'I should not necessarily be active – slow down!'	Go for walks with a girlfriend, play the piano (don't overdo it!), paint, swim, dance, phone my sister, spend time with my family, eat together.
Vaginal dryness/ reduced libido	'I am open and will wait and see what side effects I have', 'My partner and I have been able to cope with lots of other problems in the past!'	Talk about it with the partner, consultation with a gynecologist, lubricant cream.
Fatigue/ lack of motivation	'Just slow down!', 'Think about my guardian angel', 'Gratitude for so many dear people around me', 'I can allow myself to be thin-skinned'.	Lie down, listen to a relaxation CD, enjoy all the little things in life, go biking for a downhill 'shoot', listen to music, especially the song 'You Are Beautiful' by James Blunt.
Ms. Mey		
Mood swings, anxiety and anger	'I don't have to work 100%!', 'I don't always have to be the strong woman!', acceptance of anxiety; analyze: where do these feelings come from – is it anger or fear?; be mindful: estimate on a scale how strong the feelings are, 'Do I want to I want to accept the invitation to be angry?'	Imagination of a private place, use Thera-band, go outside, go for a hike, use counting for impulse control.
Weight gain	'It's not worth thinking so much about weight gain!', 'I have dealt with much worse things!', 'Protection against cancer comes first!'	Gymnastics, go jogging at least every other day, eat healthy food.

It was suggested, to highlight the image, that it might be shown in a different medium. Ms. Mey replied, however, that a drawing on an A4 sheet of paper is not sufficient to convey the power of this symbol of endocrine therapy, whereas the goal of coming to grips with the image and a reinforced elaboration of it was successful.

To strengthen Ms. Meys' experience of control, her ability to act had to be encouraged. Coping strategies were developed to prevent the large weight gain that she feared and to give her a good feeling about her body ('I've been fighting against weight gain all my life – that's the last thing I want!'). Helpful thoughts as well as specific, workable, realistic behavior plans were developed as strategies (table 2). The patient's previous mode of dealing with anxiety, which would often turn into anger, as well as with mood swings, was redirected in constructive ways. She is an 'irritable type' and explodes in many situations, which she then regrets, she says. She did not want this to get even worse with endocrine therapy. Various strategies of emotion regulation were worked out, such as techniques for mindful attention to feelings and for acceptance of anxiety, as well as methods to work off anger using the Thera-band. Both mental and practical strategies on the behavioral level were included. At the end of the session, the patient reported that it was helpful to have many alternative approaches at her disposal. 'Five years of medication is a long time and you never know what will happen. It's good to be prepared'.

Communication between doctor and patient can be highly relevant to the patient's attitude toward a recommended therapy, and, depending on the underlying placebo or nocebo mechanisms, can play a key role in the development of side effects [Colloca and Finniss, 2012]. Therefore useful strategies for communication with doctors were reviewed, e.g., that Ms. Mey could ask questions for as long as she needed in order to understand everything and that there is no such thing as 'stupid' questions. For this purpose, previous conversations with doctors were analyzed.

In the subsequent exercise for attention control and resource activation, Ms. Mey was helped therapeutically to come up with her own personal resources for the next few months. She didn't want to return to the 'rat race' of stress. For her, taking the tablet was now a daily signal to pay more attention to herself, she said.

In the refresher calls, Ms. Mey reported that she was having no side effects from the endocrine therapy, except that she had gained a bit of weight. But she said she could handle that well ('It's not worth worrying about...'). She reported that she had benefited from the program and was using lots of its content. Re-

garding side effects, she said she was better prepared and now knows that certain bodily symptoms, such as joint pain, can be just a side effect of the endocrine therapy and are not necessarily metastases.

Quantitative Case Evaluation

Results for Satisfaction and Feasibility

Absenteeism and withdrawal from therapy: Both patients attended all 3 appointments. The sessions averaged 60 minutes, and the refresher calls averaged 15 minutes.

Questionnaire evaluation: On a 6-step Likert scale from 'does not apply at all' to 'applies very much', both patients gave a rating of 'applies' or 'applies very much' to the statements that the discussions had helped them; that they had acquired specific strategies to deal with possible side effects; and that they felt better prepared for the endocrine therapy. Ms. Mey also indicated that she thought it 'applies very much' that she had received important new information about breast cancer and endocrine therapy, while Ms. Mohn considered this point 'somewhat applicable'. Both women said they would recommend the program to other breast cancer patients.

Findings about Changed Expectations and Attitudes toward Endocrine Therapy

Figure 1 shows that in the GASE-Expect questionnaire, Ms. Mohn, after the intervention, expected fewer side effects than she did before the intervention (baseline: cumulative value (CV) = 37; post-intervention: CV = 25). She further stated that on average, after the end of the SEPT program, she expected to be better able to manage side effects than before (baseline: mean (M) = 1.93; post-intervention: M = 2.09). Concerning the side effects that were worked on during the program, Ms. Mohn expected both before and after the intervention that she would have symptoms of mood swings and fatigue of medium intensity. However, she found that she could cope with both side effects 'quite well' after SEPT, whereas prior to the intervention she thought that she managed them 'rather badly'. Ms. Mohn perceived her ability to cope with the side effect of vaginal dryness both before and after the program as 'quite good'; however, after SEPT, her expectation of the intensity of the problem was reduced from 'medium' to 'mild'. At both follow-up times, Ms. Mohn expected to have mild mood swings as well as hot flashes and assumed that she would be able to cope with them 'quite well'.

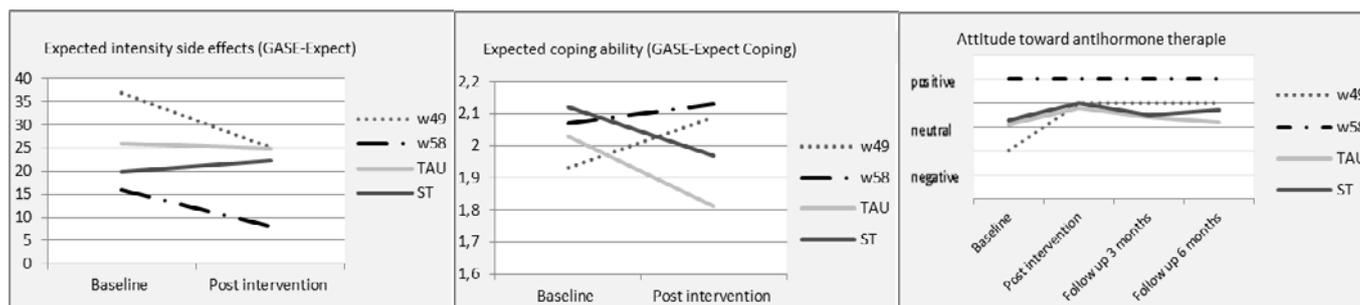


Fig. 1. Changes in attitude toward antihormone therapy and course of expectation toward side effects of Ms. Mohn (w49) and Ms. Mey (w58) as well as the control group patients in TAU (treatment as usual; $n = 28$) and supportive therapy (ST; $n = 21$). Baseline: before intervention and before antihormone therapy; post intervention: after completing 3 intervention sessions; follow-up: 3 and 6 months after antihormone therapy.

Ms. Mohn expected a 'slight' dryness of the mucous membranes, which she would be able to cope with 'quite well' after 3 months of endocrine therapy; 6 months after the start of the endocrine therapy, she no longer anticipated this side effect. However, she expected sleep disorders at this time, and thought she would be able to cope 'rather badly' with them in the future.

Ms. Mey's overall expectations of side effects also decreased at measurement point 2 after the end of the SEPT program ($CV = 16/8$). After the intervention, she also displayed, on average, increased coping expectations ($M = 2.07/2.13$). Regarding the side effects that were discussed during the intervention, Ms. Mey expected mild mood swings before the SEPT intervention and assessed her ability to cope with that side effect as 'rather poor'. After the program, she no longer expected mood swings. She also estimated her ability to cope with them should they occur as 'quite good'. She expected, both before and after the intervention, that she would have a slight weight gain and that she would cope with it 'quite well'. 3 and 6 months after the endocrine therapy began, Ms. Mey expected mild symptoms of both, side effects which she assessed herself as coping with 'quite well'.

Figure 1 shows the change in assessment of SEPT at measurement point 4 for both these patients. It is clear that Ms. Mohn gained a more positive attitude toward endocrine therapy (from 'quite negative' to 'rather positive') while Ms. Mey reported a 'positive' attitude toward the endocrine therapy at all measurement points.

For descriptive comparison, all the graphs show the values for the 28 patients (mean age 57.5 years; $SD = 10.8$; range: 28–77) who were in the TAU control condition and 21 patients (mean age = 54.9 years; $SD = 6.2$; range: 42–67) who had received ST. It is shown descriptively that Ms. Mohn, before the intervention, had higher expectations of side effects compared to the two control groups, and after the intervention her expectations were similar. Before the intervention, she expected the side effects to be worse, and after concluding the program she expected to be better able to cope with them than the patients in the two control groups. Ms. Mey's expectations of side effects were always lower than those of the control group patients; her expectations of being able to cope were similar before the intervention, and after the intervention they were higher than in the two control groups.

Findings for Side-Effect Burden and Quality of Life

The cumulative value of the intensity of the total side effects, which was recorded with the modified GASE, increased slightly for Ms. Mohn 3 months after the start of the endocrine therapy and remained stable 6 months after the start of treatment (baseline: $CV = 13$; 3-month follow-up: $CV = 17$; 6-month follow-up: $CV = 17$; fig. 2). With regard to the individual symptoms that were worked on, Ms. Mohn experienced mood swings of the same intensity as before the beginning of the endocrine therapy and stated that she was able to cope with them 'quite well'. The patient did not experience the dryness of the mucous membranes that she had expected. The patient reported 3 and 6 months after endocrine therapy that she suffered from mild fatigue and that she attributed this side effect to the medication. At both time points, Ms. Mohn reported that she was able to cope with the fatigue 'quite well'.

With Ms. Mey, the number and intensity of the total side effects did not increase ($CV = 9/8/7$). She declared in the GASE, at both measuring points, that

she had experienced a slight weight gain and mild mood swings, which she attributed to the endocrine therapy. She reported that she was able to cope 'very well' with both of these side effects.

Figure 2 shows that overall quality of life, as measured by the EORTC QLQ-C30, significantly improved for both Ms. Mohn ($M = 66.7/ 75.0/ 83.3$) and Ms. Mey ($M = 75.0/ 91.7/ 100$).

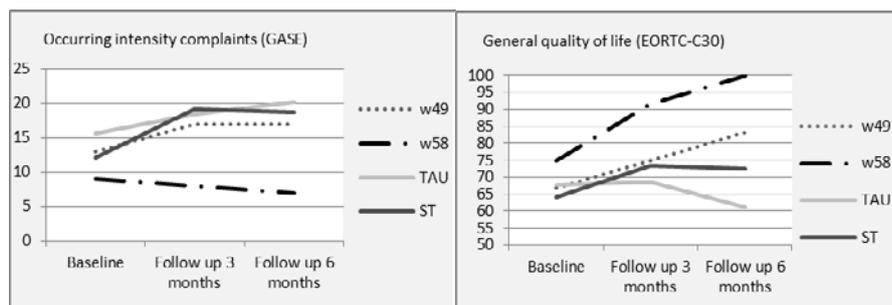
The figures also show the values for those in the control conditions, as a descriptive comparison of the side-effect burden and quality of life. Ms. Mohn at first had a side-effect burden and quality of life that was similar to that of the control groups; however, 6 months after the start of the endocrine therapy she showed a slightly lower symptom burden and a better quality of life than the patients in the control conditions. In comparison, Ms. Mey showed a lower side-effect burden and a higher increase in the quality of life compared to the patients in the control conditions.

Conclusion

On the basis of two case studies, the psychological modification of expectations for the prevention of nocebo-induced side effects was illustrated and the feasibility of the brief SEPT intervention was analyzed.

Through the qualitative case evaluation of Ms. Mohn, it became clear that a supplementary prevention program at the beginning of a long-term medication regime can positively change the patient's perspective on the treatment. For the patient with considerable prior knowledge and medical understanding, making individual coping strategies more concrete was a particularly useful means of support, to bring about greater self-efficacy. According to the motto 'Knowledge is not implementation!', the development of strategies to manage side effects in daily life and their actual implementation was the most relevant. Ms. Mey's case evaluation showed that for someone with less prior knowledge and with progressive anxiety, psychoeducation to promote understanding of the relevant illness and its treatment can be particularly helpful, to achieve, through that understanding of the medical issues, a better sense of being in control. In summary, the case studies suggest that the SEPT side effect prevention program produced positive effects for both patients. The program could be used irrespective of the patient's knowledge about the disease and its treatment, as well as independent of the person's previous attitude toward the medication. Because both patients indicated that the SEPT program was

Fig. 2. Course of intensity of side effects and the EORTC quality of life of Ms. Mohn (w49) and Ms. Mey (w58) as well as the control group patients in TAU (treatment as usual; n = 28) and supportive therapy (ST; n = 21). Baseline: before intervention and before antihormone therapy; follow-up: 3 and 6 months after antihormone therapy.



helpful and reported, in line with the therapeutic assessment, that they had benefited from various key interventions, we can infer that the program is flexible enough to be customized to the needs and requirements of different patients.

The quantitative analyses of both case studies showed a reduction in both patients of the expectation of side effects and an increase in coping expectations. This allows one to conclude that the SEPT program is achieving its goal of optimizing patients' expectations. Since at the beginning, Ms. Mohn had higher and Ms. Mey had lower expectations than average patients, it appears possible that optimization of expectations is independent of prior expectations. Furthermore, the individual case analyses suggest that experiences play an important role in expectations. Thus the expectations of both patients changed, depending on what side effects they experienced. A meta-analysis of the association between expectations and side effects shows that these associations are stronger when patients have already had experience with the treatment [Sohl et al., 2009]. This implies a special challenge for the therapeutic work, to reorient the expectations of side effects that are based on previous experiences toward a more constructive attitude. This dynamic approach to changing expectations and symptoms is facilitated by the individual refresher phone calls in the SEPT program.

With regard to the side-effect burden, Ms. Mohn's experience showed that the side effects measured by the GASE increased after the start of the endocrine therapy; she reported that this especially pertains to specific side effects. Ms. Mey reported a stable symptom burden, which suggests that the patient felt no significant incidence of side effects. Furthermore, in both case studies there was an improvement in the general quality of life. The descriptive comparisons to patients in the control groups make it clear that the patients who had no supportive discussions with psychologists during the study reported a reduction in their overall quality of life, whereas that quality of life remained stable in the patients from the ST. Since these are only preliminary results, however, the absolute values for the not-yet-completed control groups are not interpreted here. The main analysis of the effectiveness will be done after completion of the study, with a planned sample size of 153 patients.

Both the patients we analyzed reported that they felt better prepared for endocrine therapy by the SEPT program; they kept all their appointments and would recommend the program to others. From this we conclude that the program has basic feasibility and a high level of acceptance and satisfaction.

Regarding the theoretical classification, the results of both qualitative and quantitative analyses of the individual cases indicate that the modification of coping expectations, according to Leventhal's Common Sense Model of Self-Regulation, as well as the change of side effect expectations according to the nocebo model, are meaningful constructs upon which to develop a prevention program. The individual principles will have to be verified based on the full sample and analyzed, however.

Given this background, the highly relevant question of whether education about the nocebo effect would induce fear, was negated in the cases of both patients. They described it as helpful to receive information about psychological processes in the development of side effects. Ms. Mey said that she recognized her own responsibility regarding the development of side effects. This gives her a chance, she said, to become more conscious of her own attitudes and then actively to do something to help herself and improve her own quality of life. Ms. Mohn realized from the education she received about the nocebo effect that conscious scanning of her body for side effects could have negative consequences and said she wanted to reduce this. The case studies show that education about the nocebo effect can be used to promote positive behavior planning.

Nevertheless, possible undesired effects of such a program should be discussed. The question arises, whether explicitly talking about expectations and possible side effects can cause anxiety and induce side effects by a sensitization process. On the one hand, studies show that engagement with the issue of side effect expectations does not lead to increased incidence of side effects [Colagiuri et al., 2013]; on the other, warning patients about side effects can increase their occurrence [Colagiuri et al., 2012]. This aspect with regard to suitable patient education is frequently discussed in the research [Wells and Kaptchuk, 2012]. The education should be tailored to the needs of the patients and also address the protective effect of the drug. For Ms. Mey, realistic expectations should be coupled with strengthening of self-efficacy by means of the coping strategies (anti-nocebo mechanisms), rather than discussing vague, non-explicit concepts about the treatment. In individual cases, different approaches could be useful to avoid unwanted effects. Thus some patients experience as helpful the coping strategy of 'blunting' (cognitive avoidance) – i.e., they prefer not to talk about potential side effects. In these cases, it can be useful to validate the blunting strategy within the SEPT program. Precisely because these patients often have lower adherence rates, it is important to have

good support. Studies have shown that the fit is important – i.e., patients who use the blunting strategy are better off with short, basic information [Miller, 1995; [Williams Piehota et al., 2005]. For other, very anxious patients, the detailed communication of the protective effect of endocrine therapy is particularly helpful, rather than focusing on side effects. Patients who have no expectations could also benefit from SEPT. Even if the side effect expectations might initially increase as a result of the education, it would be beneficial for the patients not to be unpleasantly surprised by possible side effects and for them at the same time to develop coping strategies. Overall, the approach should be specifically reviewed for each patient and the relevant treatment knowledge should always be conveyed through an individualized ‘informed consent’ [Wells and Kaptchuk, 2012].

Although the S3 guideline for psycho-oncology recommends psychoeducation for all cancer patients regardless of their degree of distress, there could be another possible unwanted effect of the psychological intervention, in that mentally healthy patients learn from the psychological intervention what problems cancer and its treatment entail, and no longer dare to cope with this independently. Since the program focuses on self-management, such a consequence does not seem very likely, but should nevertheless be checked in individual cases. The strategy for better doctor-patient communication that was chosen as appropriate for Ms. Mey (keep asking questions until everything is understood) could have the opposite effect in patients prone to generalized anxieties, hypochondriacal tendencies or OCD. Here, too, it is important to use individualized teaching strategies. As a principle to avoid unwanted effects, a careful diagnostic evaluation should be made for each patient and each intervention.

In regard to the case reports described here, some limitations must be elaborated. The two individual cases described here are

not representative. The selection of cases was not purely random, but was carried out according to subjective criteria (such as menopausal status, prior knowledge and attitude toward endocrine therapy). It must also be noted that there was no third-party rating of the side effects and quality of life; all values are based on self-reports. Also, the control groups used for the specified descriptive comparison were not complete.

Despite these weaknesses, relevant implications for clinical practice can be derived from the case reports we have presented. Thus individual case analyses are meaningful for the training of doctors and psychotherapists and could be useful for patient education. Given that there is often insufficient time for detailed education about endocrine therapy in hospitals, the overall relevance of adjuvant treatment along with endocrine therapy for breast cancer survivors can be made clear by such case reports.

Finally, we may conclude from the case reports described, that SEPT in both cases proved a workable and appropriate program to promote positive expectations and to optimize coping with the side effects of endocrine therapy. If these results are reflected in the total sample of the study, the SEPT intervention could represent an important approach to nocebo prevention and make a valuable contribution to improving health care for women with breast cancer.

Disclosure Statement

The authors hereby declare that there are no conflicts of interest.

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