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Is it best to expect the worst? Influence of patients' side-effect expectations on endocrine treatment outcome in a 2-year prospective clinical cohort study

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Background: This study aims to determine the role of patient expectations as potentially modifiable factor of sideeffects, quality of life, and adherence to endocrine treatment of breast cancer.

Patients and methods: A 2-year prospective clinical cohort study was conducted in routine primary care with post-15 operative patients with hormone-receptor-positive breast cancer, scheduled to start adjuvant endocrine treatment. Structured patient-reported assessments of side-effects, side-effect expectations, quality of life, and adherence took place during the first week post-surgery and after 3 and 24 months of endocrine treatment.

Results: Of 111 enrolled patients, at 3 and 24 months, 107 and 88 patients, respectively, were assessed. After 2 years of endocrine treatment, patients reported high rates of side-effects (arthralgia: 71.3%, weight gain: 53.4%, hot flashes: 46.5%), including symptoms not directly attributable to the medication (breathing problems: 28.1%, dizziness: 25.6%). Pre-treatment expectations significantly predicted patient-reported long-term side-effects and quality of life in multivariate models controlling for relevant medical and psychological variables. Relative risk of side-effects after 2 years of endocrine treatment was higher in patients with high negative expectations at baseline than in those with low negative expectations (RR = 1.833, Cl 95%, 1.032-3.256). A significant interaction confirmed this expectation effect to be particularly evident in patients with high side-effects at 3 months. Furthermore, baseline expectations were associated with adherence at 24 months (r = -0.25, P = 0.006).

Conclusions: Expectations are a genuine factor of clinical outcome from endocrine treatment for breast cancer. Negative expectations increase the risk of treatment-specific side-effects, nocebo side-effects, and non-adherence. Yet, controlled studies are needed to analyze potential causal relationships. Optimizing individual expectations might be a promising strategy to improve side-effect burden, quality of life, and adherence during longer-term drug intake.

Trial registration: ClinicalTrials.gov Identifier: NCT02088710.

Key words: expectation, nocebo effect, adverse effects, quality of life, adherence, psycho-oncology

introduction

35 Drug-related side-effects are a major public health concern. They frequently cause unfavorable health and treatment outcomes, including pre-mature drug termination [1]. Current research suggests that adverse side-effects are in part caused by non-pharmacological factors such as negative expectations [2]. The nocebo effect, which refers to the side-effects reported by people taking placebo, exemplifies psychological influences on treatment tolerability [3, 4]. Research on the nocebo effect showed that side-effects can also occur to a comparable degree in the placebo group of a trial [5]. Moreover, drug-specific sideeffects have been documented in placebo groups of double-blind 45 randomized trials [6]. Verbal suggestion and negative treatment information such as disclosure of side-effects can induce adverse side-effects in people not taking placebo but active medication, thereby eliciting nocebo-related responses during active drug treatments [7, 8].

Adjuvant endocrine therapy (AET) is the standard of care for hormone-receptor-positive breast cancer, associated with improved disease-free survival and time to recurrence [9]. While the optimal duration of endocrine therapies, alone or sequential, remains an area of active investigation, latest evidence 55

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demonstrated incremental benefits of 10 years of tamoxifen compared with a 5-year regimen [10]. However, non-adherence during the 5-year intake period ranges from 22% to 55% [11, 12]. Adverse side-effects that negatively affect quality of life constitute the main reason for non-adherence. Thus, research into potentially modifiable determinants of side-effects such as patient expectations seems promising to promote quality of life and adherence in breast cancer survivors undergoing AET.

Individual expectations of side-effects have been associated with cancer treatment side-effects [13], specifically with the non-specific toxic effects of chemotherapy such as nausea, pain, and fatigue [14]. However, implications are restricted because only few studies controlled for a prior history of symptoms or examined long-term effects. Further limitations include homogeneity of samples from randomized trials, a lack of real-world studies, and underreporting of non-serious side-effects, especially regarding patient-reported outcomes [15]. Until now, no study has analyzed the influence of expectations on side-effects of AET. This is particularly surprising since AET is the most frequently prescribed oral anti-cancer agent worldwide [16].

This study aims to quantify the impact of side-effect expectations on actual side-effects, quality of life, and adherence within a naturalistic 2-year prospective cohort study of AET for breast cancer. Patient-reported side-effects are assessed adopting the recommended terminology for reporting and grading drug adverse effects [17, 18] controlling for relevant factors such as baseline symptoms. A deeper understanding of patients' expectations about the side-effects of AET might lead to new strategies to ameliorate side-effects and promote adherence, ultimately reducing morbidity and mortality for breast cancer survivors.

materials and methods

subjects

Eligible patients were identified by the hospitals' patient-registry and tumor board review. Inclusion criteria were: diagnosis of primary breast cancer, estrogen-hormone-receptor-positive, surgery for breast cancer, recommendation for AET, female, 18–80 years, literate, no comorbid severe mental disorders (addiction or schizophrenia), or life-threatening physical impairments.

study design

Consecutive recruitment took place during routine primary care at a University Breast Cancer Center from January 2011 to March 2012; followups were collected from May 2011 to May 2014. Eligibility was assessed within 7 days following breast surgery. Consented patients received standardized verbal and written information on mechanisms, benefits, and potential side-effects of AET before treatment start. An information leaflet depicting explicit benefit and risk information, including natural frequencies of the 18 most common and most serious side-effects of AET, was handed out and discussed [19]. Treatment information was conducted face to face by trained professionals using a script. One-time sessions lasted ~15 min. They were aimed at homogenizing pre-treatment information to avoid uncontrolled influences on side-effect expectations and were conducted in an encouraging manner. The primary investigator (YN) did trainings and supervision with audio records. Assessments took place at the hospital before start of AET and 3 and 24 months after start of AET via mailed questionnaires. Dropouts were contacted to assess adherence status. Ethical approval was given by the ethics committee for medical research of the University of Marburg.

assessment

Side-effects and baseline symptoms were assessed using the modified General Assessment of Side-effects Scale (GASE) [17]. Patients rated the severity of 44 symptoms during the last week on a Likert scale (0, not present; 1, mild; 2, moderate; 3, severe), including 21 AET-specific [9, 20], and 23 non-specific symptoms, not directly attributable to the pharmacologic action of AET. Cronbach's α ranged between α = 0.87 and α = 0.91.

Side-effect expectations were measured with a modified GASE, assessing expected intensities for each potential side-effect on visual analog scales (length = 50 mm), from 'not at all' to 'maximum intensity'. Overall expectation was measured on a Likert scale (0, not expected; 1, expected side-effects mild intensity; 2, moderate; 3, severe). Cronbach's α was α = 0.96.

Health-related Quality of Life (HrQoL) was measured with the Questionnaire of the European Organization for Research and Treatment of Cancer (EORTC/QLQ-C30). A total score for all 30 items was calculated and transformed linearly to a range from 0 to 100, with high values indicating better HrQoL [21]. Cronbach's *α* ranged from α = 0.93 to α = 0.95.

Adherence was measured with a pre-validated patient self-report score [12].

Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale. Cronbach's α was $\alpha=0.82$ (anxiety) and $\alpha=0.86$ (depression).

sociodemographic and medical characteristics. Age, weight, height, education, marital, and employment status were obtained in semi-structured interviews. Stage of cancer (UICC), menopausal status, primary, and adjuvant treatments were collected from medical charts. Comorbid chronic medical illnesses during the last year were assessed with the revised Schedules for Clinical Assessment in Neuropsychiatry and verified with medical charts.

Statistical analyses were carried out using SPSS 20.0. No item had a rate of missing values higher than 1.9%. Missings were distributed completely at random (Little's MCAR test P > 0.05) and imputed with multiple imputations using NORM 2.03. Hierarchical multiple linear regression analyses were computed with a priori hypothesized sociodemographic and medical variables, baseline symptoms, and psychological parameters entered within the first three steps, and baseline side-effect expectations within the fourth step. Power calculations for the specific increase in R^2 in a multiple regression with 9 predictors resulted in 103 patients, given moderate effects, $\alpha = 0.05$, and $\beta = 0.80$. To test the interaction of expectations and side-effects over time, an ANCOVA of side-effects at 24 months was calculated using baseline expectations and side-effects at 3 months as fixed factors. Expectations and side-effects were dichotomized by categorizing none or mild versus moderate or severe intensities. Relative risks, relative risk reduction, and numbers-needed-to-treat were calculated from crosstabs.

results

participants

Of 270 patients screened, 191 met inclusion criteria. A total of n = 111 signed informed consent and were enrolled (Figure 1). Three and 24 months after start of AET, n = 107 and n = 88 patients were assessed, with respective attrition rates of 3.6% and 17.8%. Reasons for drop-out were exhaustion (n = 8), unavailability (n = 7), stop of AET (n = 3), medical reasons (n = 3), and death (n = 2). Comparisons of drop-outs and completers revealed no significant differences in sociodemographic or clinical characteristics. Baseline characteristics of the analyzed sample (n = 111) are given in Table 1.

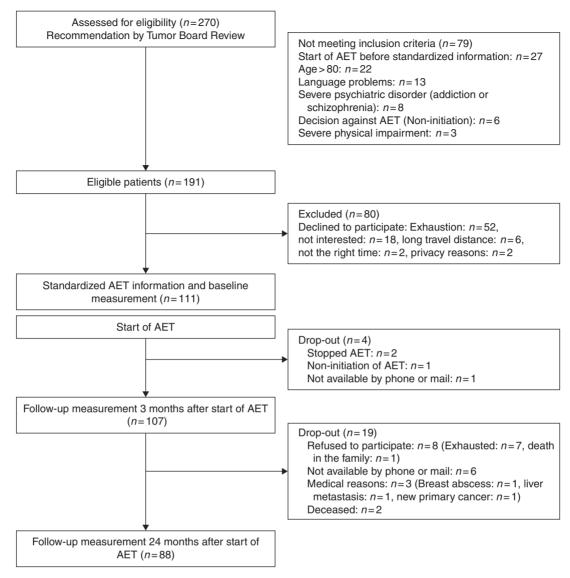


Figure 1. Patients flow. AET, adjuvant endocrine therapy.

expectations of side-effects

At baseline, nine patients (8.1%) reported to expect no side-effects from AET. Mild side-effects were expected by 70 patients (63.1%); 32 patients (28.8%) expected moderate to severe side-effects. Drop-out was significantly higher in patients with moderate or severe side-effect expectations than in patients reporting none or mild expectations [$\chi^2(1,111) = 3.034$, P < 0.05]. The overall intensity of expected side-effects was rated mild to moderate (range = 0–3, M = 1.23, SD = 0.6).

side-effects and HrQoL at follow-up

Baseline-controlled event rates for side-effects at 24 months were highest for arthralgia (71.3%), weight gain (53.4%), and myalgia (50.6%). Notably, a number of non-specific symptoms such as back pain (31%), breathing problems (24.7%), and palpitations (20.7%) were reported (Figure 2). Supplementary Table S1, available at *Annals of Oncology* online, depicts rates for all time-points. The mean number of moderate or severe symptoms increased

significantly from baseline (M = 3.55, SD = 3.96) to 3 months [M = 6.07, SD = 6.10, $t_{3 \text{ months}}(106) = -5.292$, P < 0.01] and to 24 months [M = 6.81, SD = 7.28, $t_{24 \text{ months}}(87) = -3.277$, P < 0.01). At 3 months, patients who dropped out later on (n = 19) reported significantly more side-effects than completers (n = 88) [t(105) = 3.398, P < 0.001]. Serious adverse events were recorded for seven patients (cardiopulmonary syndromes, bleeding problems). HrQoL increased from baseline (M = 69.91, SD = 18.59) to 3 months [M = 74.31, SD = 20.70, t(106) = -2.532, P < 0.05] and remained stable until 24 months (M = 78.33, SD = 20.03).

adherence to AET

At 24 months, 68 women (61.3%) reported full adherence. Eighty percent adherence was reported by 11 patients (9.9%). Seventeen patients (15.3%) reported non-adherence, of these, 15 had discontinued completely. Owing to patient drop-out and unavailability, adherence-status remained unknown in 13 patients (11.7%). Two patients were deceased (1.8%).

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Table 1. Patients' sociodemographic and medical characteristics							
Characteristics	n = 111 [n (%)]						
Age in years (mean, SD, range)	55.5 (11.0, 26–79)						
Marital status							
Married/partnership	81 (73)						
Divorced/widowed/single	30 (27)						
Education							
Primary/secondary education	89 (80.2)						
Higher education	22 (19.8)						
Work status							
Employed	62 (55.9)						
Not employed	49 (44.1)						
Menopausal status							
Pre-menopausal	32 (28.8)						
Post-menopausal	76 (68.5)						
Perimenopausal	3 (2.7)						
BMI^a							
Mean BMI (SD, range)	26.92 (5.64, 18.4–50.2)						
Underweight (BMI < 18.5)	1 (0.9)						
Normal (BMI: 18.5–30)	91 (82)						
Obese (BMI > 30)	19 (17.1)						
Mamma carcinoma							
First diagnosis	108 (97.3)						
Recurrence	3 (2.7)						
Tumor stage							
0	3 (2.7)						
I	58 (52.3)						
II	34 (30.6)						
III	14 (12.6)						
IV	2 (1.8)						
Surgery	, ,						
Mastectomy	21 (18.9)						
Breast-conserving	90 (81.1)						
Adjuvant medical therapy	· · /						
Chemotherapy	33 (29.7)						
Radiotherapy	102 (91.9)						
Endocrine therapy	· · · /						
Tamoxifen	46 (41.4)						
Aromatase inhibitor	60 (54.1)						
Switch	5 (4.5)						
Comorbid chronic conditions	,,						
None	36 (32.4)						
1–2 comorbid conditions	52 (46.8)						
3–5 comorbid conditions	23 (20.7)						
HADS at baseline (mean, SD)	()						
Depression	3.35 (3.49)						
Anxiety	5.39 (3.83)						

SD, standard deviation; BMI, body mass index; Switch, switch from tamoxifen to aromatase inhibitor.

^aReduced n = 95, 16 women did not specify weight. Most common comorbid chronic conditions were hypertension (33.3%), thyroid dysfunction (27%), back pain (19%), and coronary heart diseases (12%).

correlates of side-effects and expectations (only significant correlations of $r \ge 0.3$ are reported)

Side-effects at 3 months were significantly correlated with baseline side-effect expectations [r = 0.336 (107), P < 0.001], anxiety [r = 0.477 (107), P < 0.001], and depression [r = 0.464 (107),P < 0.001]. Side-effects at 24 months were correlated with baseline expectations [r = 0.340 (88), P = 0.001]. No associations with other clinical variables such as staging, type of AET, or adjuvant chemotherapy resulted.

Adherence at 24 months was correlated with side-effects at 3 months [r = -0.407 (93), P < 0.001], and small but significantly with baseline side-effect expectations [r = -0.254 (96), P = 0.006].

prediction models of side-effects and HrQoL

Significant regression models resulted for baseline expectations on long-term side-effects (Table 2). Patients' age, menopausal status, cancer stage, type of AET, depression, and anxiety did not contribute significantly, comorbid conditions were significant predictor at 3 months. Baseline symptoms resulted as significant predictor at 3 and 24 months. Patients' baseline expectations predicted significant incremental variance components at 3 months $(\Delta R^2 = 0.03, P = 0.023)$ and 24 months $(\Delta R^2 = 0.06, P = 0.018)$. Higher expectations predicted a higher occurrence of side-effects $(\beta_{3 \text{ months}} = 0.19, P = 0.023; \beta_{24 \text{ months}} = 0.26, P = 0.018).$ The final models explained 40% [$F_{3 \text{ months}}(9,97) = 8.856$, P < 0.001] and 17% of variance $[F_{24 \text{ months}} (9,78) = 2.905, P = 0.006]$.

The same analysis plan was used to predict HrQoL, with baseline HrQoL as control variable. Age, menopausal status, staging, comorbid conditions, anxiety, and depression did not contribute significantly. Baseline EORTC scores resulted as significant predictors in both models. Side-effect expectations explained an additional 4% of HrQoL at 3 months. At 24 months, a trend emerged. Higher expectations of side-effects predicted lower HrQoL ($\beta_{3 \text{ months}} = -0.22$, P = 0.007; $\beta_{24 \text{ months}} = -0.19$, P = 0.101). The final models explained 42% [$F_{3 \text{ months}}(9,97) =$ 9.579, P < 0.001 and 19% of variance $[F_{24 \text{ months}}(9,77) = 3.224,$ P = 0.002].

relative risk of side-effects

Side-effects at 24 months were significantly higher in patients with highly negative expectations at baseline (M = 10.64, SE = 1.25) than in those with low negative expectations (M = 6.62, SE = 0.375). An ANCOVA revealed this difference to be significant after controlling for baseline symptoms and anxiety [F(1,82) = 7.565; $\eta_p^2 = 0.08$] (Figure 3). Side-effects at 24 months were significantly higher in patients with high side-effects at 3 months (M = 12.85, SE = 1.15) than in patients with low initial side-effects [M = 4.41], SE = 0.93; F(1,82) = 31.245; $\eta_p^2 = 0.28$]. Furthermore, there was a significant interaction of expectations and 3 months side-effects $[F(1,82) = 5.507; \eta_p^2 = 0.06].$

Crosstab analysis resulted in significant relative risks of sideeffects at 3 months (RR = 1.672, CI 95% 1.073-2.605) and 24 months (RR = 1.833, CI 95% 1.032-3.256) corresponding to moderate to large relative risk reductions (RRR_{3 months} = 0.40; $RRR_{24 \text{ months}} = 0.45$) and a number-needed-to-treat of 4.4.

discussion

This was a prospective cohort study with high external validity and a 2-year follow-up. Results confirmed that the incidence of side-effects over 2 years of AET was prospectively influenced by patients' side-effect expectations as opposed to medical factors.

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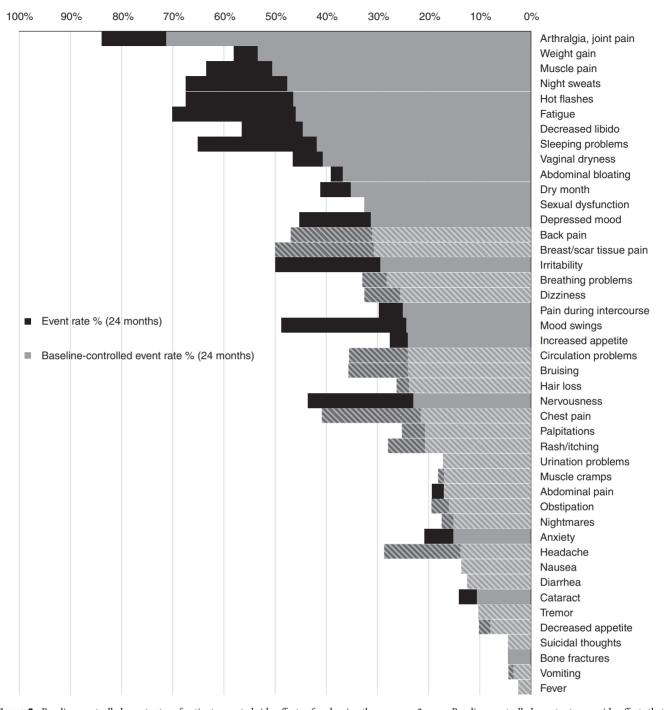


Figure 2. Baseline-controlled event rates of patient-reported side-effects of endocrine therapy over 2 years. Baseline-controlled event rates are side-effects that either newly occurred or exacerbated within 24 months of adjuvant endocrine therapy in relation to baseline symptom rates. Solid bars represent specific side effects, striped bars are non-specific side-effects. Non-specific side-effects are not directly attributable to the pharmacologic action of the drug and are not included in patient information as potential side-effects of endocrine therapy.

Nocebo-related effects accounted for a risk reduction of 45%. In other words, women holding negative or highly negative expectations about the side-effects of AET before treatment start experienced almost twice the side-effects than those with positive or low negative expectations. This expectation effect increased over time and was particularly evident in patients reporting high rates of side-effects after the first 3 months. Furthermore, expectations about side-effects of AET predicted HrQoL and were associated with adherence, although only with

a small effect. This finding is of high clinical relevance since non-adherence to AET predicts lower survival [22].

Event rates for arthralgia, menopausal, and gynecologic symptoms from this study were higher than those documented in randomized, controlled trials of AET [20, 23]. Yet, comparable or even higher rates for gynecologic symptoms and sexual dysfunction were reported from other real-life studies using prespecified patient-reported outcomes [24, 25]. Interestingly, the women in this study reported considerable rates of non-specific

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	Predictors	Side-effect total score 3 months follow-up		Side-effect total score 24 months follow-up				
		$r_{\mathrm{un-adj.}}$	β	ΔR^2	$r_{\mathrm{un-adj.}}$	β	ΔR^2	
Step 1	Age	-0.015	-0.022	0.02	-0.194	-0.225	0.05	
	Menopausal status	0.009	-0.117		-0.061	0.007		
	Staging	-0.124	0.025		-0.096	-0.077		
	Type of AET	0.027	-0.049		0.169	0.055		
Step 2	Baseline symptoms	0.546**	0.548**	0.36**	0.367**	0.353**	0.12**	
	Comorbid conditions	0.250**	0.231*		0.022	0.060		
Step 3	Depression	0.464**	0.102	0.04*	0.040	-0.212	0.02	
	Anxiety	0.477**	0.182		0.213*	0.176		
Step 4	Expectation of side-effects	0.336**	0.191*	0.03*	0.340**	0.261*	0.06*	
R2 (Adjust	R^2			0.45 (0.40)			0.25 (0.17	
		$F(9,97) = 8.856^{**}$				F(9,78)	$F(9,78) = 2.905^{**}$	

n = 107 at 3 months follow-up, n = 88 at 24 months follow-up.

 $r_{\text{un-adj}}$, unadjusted bivariate correlations; β , standardizes regression coefficients; ΔR^2 , incremental proportion of variance explained by each regression step; AET, adjuvant endocrine therapy: tamoxifen versus aromtase inhibitors.

^{*}P < 0.05, **P < 0.01.

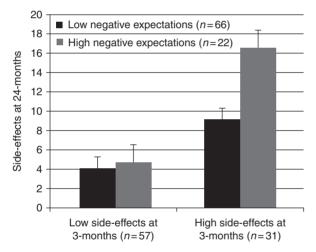


Figure 3. Reported side-effects after 24 months of AET of patients with high and low expectations and high and low initial side-effects at 3 months. Side-effects at 24 months = mean number of moderate or severe side-effects after 24 months of endocrine treatment. Main effect expectation: side-effects of endocrine treatment at 24 months are significantly higher in patients with highly negative expectations at baseline, than in patients with low negative expectations $[F(1,83) = 7.797; \ \eta_{\rm P}^2 = 0.09]$. Main effects initial side-effects: side-effects of endocrine treatment at 24 months are significantly higher in patients with high initial side-effects (3 months response), than in patients with low initial side-effects $[F(1,83) = 39.096; \ \eta_{\rm P}^2 = 0.32]$. Interaction: side-effects are higher in patients with negative expectations and initially high side-effects $[F(1,83) = 7.385; \ \eta_{\rm P}^2 = 0.08]$. Baseline symptoms and anxiety were used as covariates. **P < 0.01.

side-effects such as breathing problems, palpitations, and rash. This substantiates the conclusion that psychological mechanisms like expectation-related nocebo effects play a significant role in AET for breast cancer survivors. Negative expectations, formed by patients before the start of AET, seem to have a pronounced influence on patient-reported long-term tolerability,

once they are confirmed by initially high side-effects. Whereas negative baseline expectations that are violated by contrasting experiences of low side-effects after the first 3 months of AET seem to cease their negative impact. Hence, expectation-modification interventions might be especially promising for patients with negative expectations who initially report high side-effects. Expectations as iatrogenic factors can be modified by psychological interventions [2, 5]. Therapeutic strategies aimed at reducing nocebo-related side-effects might include psychoeducation using beneficial information framing methods [26], optimizing coping expectations, and symptom reattribution such as encouraging patients to view potential side-effects not as purely bothersome complaints but as a signal that the therapy starts to exert its beneficial effect [27, 28].

With regard to limitations, this naturalistic cohort did not include a control group. Although confounding factors like symptoms introduced by medical comorbidities, concurrent treatments, age, or cancer staging were controlled statistically, future studies might strengthen causal implications by experimentally inducing expectations about cancer treatments. The standardized AET-information was used to harmonize patients' informational status. However, we were unable to control additional sources like the Internet, friends, and families who might have provided information about AET and shaped expectations. The AET-information might have fostered adherence [19], thereby restricting generalizability to other samples. Furthermore, generalizability might be limited by the fact that nearly 40% of eligible patients declined participation. Specifically, patients with dysfunctional expectations about AET or low adherence might have declined participation, since they were more likely to drop out of the study. Thus, in an unselected sample, side-effect expectations might result more negative and adherence rates lower than reported here. Lastly, the relationship of expectations and adherence warrants replication.

This study showed that a significant proportion of reported side-effects from AET is determined by patients' expectations

and therefore attributable to non-pharmacological mechanisms like the nocebo effect. This raises the question how expectations are formed and whether they can be remediated. Future studies should target expectations and explore their longitudinal relationship to side-effects and adherence, possibly including non-self-report measures. Furthermore, research is needed to quantify the effects of treatment information on cancer patients' expectations, and to evaluate how best to communicate possible side-effects in order to prevent nocebo-related symptoms [29].

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disclosure

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