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# Beta-blockers may reduce intrusive thoughts in newly diagnosed cancer patients

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## Abstract

***Objective*: A cancer diagnosis provokes significant levels of emotional distress, with intrusive thoughts being the most common manifestation among breast cancer survivors. Cancer-related intrusive thoughts can take the form of emotional memories, flashbacks, nightmares, and intrusive images. Emotional arousal after a severe life stressor prolongs adrenergic activation, which in turn may increase risk for post-traumatic symptomatology. However, antihypertensive beta-blockers block adrenergic activation and are known to reduce traumatic memories and related psychological distress. Thus, the current study examined the association between beta-blocker use and the severity of cancer-related intrusive thoughts and related symptoms following a cancer diagnosis.**

***Methods*: The 174 breast and 36 female colorectal cancer patients who had recently undergone diagnostic screening or biopsy included 39 beta-blocker users and 171 non-users. Prior to any cancer treatment including surgery, participants completed questionnaires that included the Impact of Events Scale and the Center for Epidemiological Studies Depression Scale. Analyses controlled for age, education, cancer stage, cancer type, days since diagnosis, marital status, depression, and comorbidities.**

***Results*: Although the high rates of cancer-related distress in this sample were similar to those of other studies with recently diagnosed patients, beta-blocker users endorsed 32% fewer cancer-related intrusive thoughts than non-users.**

***Conclusions*: Recently diagnosed cancer patients using beta-blockers reported less cancer-related psychological distress. These results suggest that beta-blocker use may benefit cancer patients' psychological adjustment following diagnosis, and provide a promising direction for future investigations on the pharmacological benefits of beta-blockers for cancer-related distress.**



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## Introduction

A cancer diagnosis provokes significant levels of emotional distress, with intrusive thoughts being the most common manifestation among breast cancer survivors [1–4]. Cancer-related intrusions include recurrent or distressing thoughts or dreams about cancer, unintentional thoughts about cancer, and high levels of distress when reminded about cancer [4]. Post-traumatic stress disorder (PTSD) is characterized by similar re-experiencing symptoms, as well as symptoms of avoidance and hyperarousal [5]. Emotional memories, flashbacks, nightmares, and intrusive images produce considerable distress, and stimuli associated with the trauma are persistently avoided. Re-experiencing is a result of fear conditioning and thus is an important indicator of post-traumatic psychological distress [6].

Emotionally arousing experiences increase noradrenergic activity [7]. Prolonged adrenergic activation in the immediate aftermath of a major stressor may increase risk for PTSD [5]. In particular, excess epinephrine while emotionally aroused enhances the formation of traumatic memories [8]. Propranolol is one class of beta-adrenergic blockers commonly used in the treatment of hypertension. Administration of propranolol soon after a trauma reduces memory for the event and is thought to consequently prevent the development of PTSD [5]. This may occur in part because propranolol interferes with stress-related neural activity [9].

Propranolol reduced the strength of newly acquired emotional memories in experimental studies [10], and similar effects were observed in some trauma-exposed clinical samples [8,11,12], although there are some exceptions [13,14]. Furthermore, clinical trials reveal that PTSD symptomatology decreased when patients were re-exposed to the trauma while taking propranolol [15,16]. A prospective observational study with cardiac surgery patients showed that a beta-adrenergic antagonist reduced traumatic memories and PTSD symptoms in women [8]. These findings raise the provocative possibility that beta-blockers could impede the development of intrusive thoughts and related symptoms following a cancer diagnosis. Accordingly, the current study addressed the association between beta-blocker use and the severity of intrusions following a cancer diagnosis. It was expected that beta-blocker use would be related to fewer cancer-related intrusive thoughts.

## Methods

### Sample

We screened electronic medical records linked to The Ohio State University Medical Center for participants who were seen at outpatient surgical oncology or mammography clinics. Female breast and colorectal cancer patients ($n = 210$) were recruited during 2009–2011 within 1–3 months following their cancer diagnosis. Screening exclusions included a prior history of any cancer except basal or squamous cell skin cancers. Once they were deemed eligible, we contacted them by phone. They completed a questionnaire battery and blood draw prior to any cancer treatment, including surgery. Of these women, 39 were taking a beta-blocker medication for hypertension according to medical records. This information was cross-referenced with participant self-reported indication and use for beta-blocker medication. The data were drawn from an observational study investigating the links between inflammation and fatigue in both colorectal and breast cancer patients. The Ohio State University Institutional Review Board approved the project, and all subjects gave written informed consent prior to participation.

### Measures

The 15-item Impact of Events Scale (IES) [17] assessed participant's avoidant and intrusive thoughts regarding their recent diagnostic screening tests. For these women, diagnostic screening tests included mammography, colonoscopy, and ultrasound-guided biopsy. The IES, which has separate avoidant and intrusive subscales, is commonly used to assess cancer-related psychological distress [18]. Participants were asked to indicate how frequently each item had been true in the preceding week. Sample intrusion items include 'Pictures about it popped into my head', and 'I had waves of strong feelings about it'. Avoidance items include 'I tried not to talk about it', and 'I felt as if it hadn't happened or wasn't real'. Responses to items are rated on a scale from 0 (not at all) to 5 (often).

The Charlson Index [19], a widely used comorbidity measure, assesses 19 comorbid conditions. Each is assigned a weight according to its potential to influence 1-year mortality. The final index is a sum of the weighted comorbidities, which accounts for the number and seriousness of the conditions. Originally developed for predicting mortality in breast cancer patients, it has now been widely used with both cancer and noncancer populations [20]. Data for this index were obtained from patient chart review.

The 20-item Center for Epidemiological Studies Depression Scale [21] has been used extensively as a brief measure of depressive symptomatology [22]. Items including 'I felt that everything I did was an effort' and 'I felt depressed' are rated for their frequency in the last week, using a scale from 0 (rarely or none of the time) to 3 (most or all of the time).

The Beck Anxiety Inventory [23] assesses both cognitive and physiological symptoms of anxiety (e.g., hands trembling or fear of losing control). This measure was developed to discriminate anxiety from depression, and severity of symptoms is rated on a scale from 0 (not at all) to 3 (severely).

### Statistical analyses

Using separate ordinary least squares general linear models in SPSS (SPSS Inc., Chicago, IL), we addressed the question of whether beta-blocker use was associated with cancer screening-specific intrusions in our sample of newly diagnosed female breast and colorectal cancer patients. In this analysis, we ran both unadjusted and adjusted regression models. In the first step of our adjusted regression model, we entered a number of potential confounds: age, education, cancer stage, cancer type, time since diagnosis (days), and marital status (1 = partnered, 0 = not partnered). Depression scores were included in the second step to assess their influence on intrusions [24]. To address the added impact of having previously existing risk factors for mortality on cancer screening-related distress, the number of comorbidities was entered as the third step. Beta-blocker medication use was entered as the fourth and final step. All tests used a two-sided, $\alpha = 0.05$ significance level.

## Results

### Descriptive characteristics of the sample

Table 1 provides descriptive information for the sample. Comparisons were made between beta-blocker users ($n = 39$) and non-users ($n = 171$). Beta-blocker users were significantly older than non-users ($F(1, 209) = 35.99$, $p < 0.01$). Compared with non-users, users were more likely to be without a partner ($F(1, 209) = 5.49$, $p < 0.05$), not currently employed ($X^2(4) = 19.185$, $p < 0.01$), and to have a lower income ($F(1, 184) = 10.91$, $p < 0.01$). Other than reporting a greater number of comorbidities ($F(1, 209) = 30.31$, $p < 0.01$), beta-blocker users were not significantly different from non-users on any additional clinical or psychological characteristics (Table 2). No significant correlations between the group demographic differences and intrusions were identified. Furthermore, because beta-blocker use or number of intrusions did not differ between the breast and colorectal patients, these groups were combined in the regression analyses.

The psychological impact of beta-blockers may depend on their relative lipid-solubility, as lipophilic compositions might have more direct central nervous system effects [8]. However, the lipid-solubility of the various beta-blockers did not impact intrusion scores. Specifically, levels of intrusive thoughts did not differ between women using lipid-soluble beta-blockers ($n = 7$) or water-soluble beta-blockers ($n = 32$).

Beta-blocker use was associated with fewer intrusions in both the unadjusted and adjusted regression models (Table 3). The linear combination of age, education, marital status, time since diagnosis, cancer stage, cancer type, depression, comorbidities, and beta-blocker use accounted for a 42.5% (adjusted $R^2$) of the total variance in intrusions. Relative to non-users, women using beta-blockers reported 32% fewer cancer-related intrusions. In ancillary analyses, these results did not change when anxiety scores were substituted for depression in the same model, nor did results change when employment status and income level were also included in step one. Additionally, beta-blocker use was not related to scores on the IES Avoidance subscale, and interactions with age and depression were not significant.



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**Table 1.** Descriptive statistics for the total sample and by beta-blocker use

| | Total sample ($N = 210$) | | Beta-blocker ($N = 39$) | | No beta-blocker ($N = 171$) | |
|---|---|---|---|---|---|---|
| **Characteristic** | **Number** | **%** | **Number** | **%** | **Number** | **%** |
| Age Mean + SD (years)** | 55.98 | (12.94) | 66.36 | (13.02) | 53.61 | (11.72) |
| Ethnicity | | | | | | |
| White | 178 | 84.8 | 30 | 76.9 | 148 | 86.5 |
| Black | 25 | 11.9 | 8 | 20.5 | 17 | 9.9 |
| Asian | 4 | 1.9 | 0 | – | 4 | 2.3 |
| Native American | 1 | 0.5 | 0 | – | 1 | 0.6 |
| Latino | 4 | – | 0 | – | 4 | – |
| Other | 2 | 1.0 | 1 | 2.6 | 1 | 0.6 |
| Marital status** | | | | | | |
| Married/Dom. partner | 136 | 64.8 | 19 | 48.7 | 117 | 68.4 |
| Separated/ Divorced | 26 | 12.4 | 7 | 18.0 | 19 | 11.1 |
| Single | 28 | 13.3 | 3 | 7.7 | 25 | 14.6 |
| Widowed | 20 | 9.5 | 10 | 25.6 | 10 | 5.8 |
| Education level | | | | | | |
| High school or less | 66 | 31.4 | 16 | 41.0 | 50 | 29.2 |
| ≥Some College | 144 | 68.6 | 23 | 59.0 | 121 | 70.8 |
| Employment status** | | | | | | |
| Full or part time | 115 | 54.7 | 15 | 38.5 | 100 | 58.5 |
| Unemployed/Disability | 46 | 21.9 | 6 | 15.3 | 40 | 23.4 |
| Retired | 49 | 23.3 | 18 | 46.2 | 31 | 18.1 |
| Income level* | | | | | | |
| <$50,000 | 84 | 40.0 | 23 | 59.0 | 61 | 35.6 |
| ≥$50,000 | 101 | 48.1 | 10 | 25.6 | 91 | 53.3 |
| Prefer not answer | 25 | 11.9 | 6 | 15.4 | 19 | 11.1 |
| Cancer type | | | | | | |
| Breast | 174 | 82.9 | 32 | 82.1 | 142 | 83.0 |
| Colorectal | 36 | 17.1 | 7 | 17.9 | 29 | 17.0 |
| Cancer stage | | | | | | |
| Stage 0 | 29 | 13.8 | 4 | 10.3 | 25 | 14.6 |
| Stage I | 72 | 34.3 | 15 | 38.5 | 57 | 33.3 |
| Stage IIA | 43 | 20.5 | 7 | 17.9 | 36 | 21.1 |
| Stage IIB | 19 | 9.0 | 4 | 10.3 | 15 | 8.8 |
| Stage III | 27 | 12.8 | 4 | 10.3 | 23 | 13.5 |
| Stage IV | 20 | 9.5 | 5 | 12.8 | 15 | 8.8 |

*$p < 0.05$.
**$p < 0.01$.

**Table 2.** Mean (±SD) scores on clinical and psychological variables for the total sample and as a function of beta-blocker medication use

| | Range | Total sample | Beta-blocker | No beta-blocker |
|---|---|---|---|---|
| Time since diagnosis (days) | 0–69 | 23.68 (14.29) | 26.36 (14.41) | 23.06 (14.24) |
| No. of Charlson-rated comorbidities** | 0–8 | 0.74 (1.43) | 1.54 (2.01) | 0.56 (1.20) |
| CES-D total score | 0–49 | 15.97 (10.63) | 13.41 (11.35) | 16.49 (10.40) |
| BAI total score | 0–40 | 11.66 (8.91) | 10.67 (9.28) | 11.88 (8.84) |
| IES Avoidance score | 0–40 | 16.87 (8.96) | 17.28 (9.35) | 16.78 (8.89) |
| IES Intrusion score** | 0–35 | 14.94 (9.14) | 10.79 (8.33) | 15.89 (9.08) |

CES-D, Center for Epidemiological Studies Depression Scale; BAI, Beck Anxiety Inventory; IES, Impact of Events Scale.
*$p < 0.05$.
**$p < 0.01$.

## Discussion

In this sample, beta-blocker users reported 32% fewer intrusive thoughts than non-users. This effect was significant both in the unadjusted model and in the adjusted model that controlled for a number of relevant covariates including age, which is important given that beta-blocker users were older and age has been associated with reduced distress after cancer [25]. These data suggest that beta-blocker use may attenuate the severity of cancer-related intrusions among newly diagnosed breast and colorectal cancer patients.

Our participants' rates of intrusive thoughts were similar to those reported in other studies of recently diagnosed breast patients [1–3]. It should be noted that only a small number of investigations have examined these kinds of cancer-related stress responses immediately following diagnosis. Many additional studies have reported a low incidence of post-traumatic intrusions among cancer patients [25–27]. However, these studies were mostly of patients' post-treatment intrusions, and in some, assessment occurred up to 3 years after diagnosis [26–28]. Our study provides further evidence that intrusive symptoms may be especially severe within the first month following diagnosis.



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**Table 3.** Summary of unadjusted and adjusted regression models predicting intrusions from beta-blocker use

| Model | Step and variables | $\beta$ | $\Delta R^2$ | *SE* | 95% Confidence interval |
|---|---|---|---|---|---|
| Unadjusted | Beta-blocker use | −5.094 | | 1.588 | [−8.244 to −1.964] |
| | $R^2$ | 0.043** | | | |
| | $F(1, 208)$ | 10.293** | | | |
| Adjusted | Step 1 | | | | |
| | Age | −0.212 | 0.109** | 0.047 | [−0.306 to −0.119] |
| | Education | 0.165 | | 0.473 | [−0.767 to 1.098] |
| | Marital status | −0.258 | | 1.300 | [−2.821 to 2.305] |
| | Time since diagnosis | −0.069 | | 0.043 | [−0.154 to 0.016] |
| | Cancer stage | −0.240 | | 0.312 | [−0.855 to 0.374] |
| | Cancer type | −0.217 | | 1.727 | [−3.622 to 3.189] |
| | Step 2 | | | | |
| | Depression | 0.520 | 0.325** | 0.048 | [0.424–0.615] |
| | Step 3 | | | | |
| | Comorbidities | 0.343 | 0.002 | 0.463 | [−0.528 to 1.297] |
| | Step 4 | | | | |
| | Beta-blocker use | −3.122 | 0.014* | 1.382 | [−5.848 to −0.396] |
| | $R^2$ | 0.425** | | | |
| | $F(9, 200)$ | 18.193** | | | |

Parameters are reported as unstandardized coefficients.
*$p < 0.05$.
**$p < 0.01$.

Moreover, as was seen in our sample, beta-blockers appear to mitigate psychological distress at a time when it is particularly heightened.

Intrusive thoughts and re-experiencing symptoms maintain post-traumatic stress-like symptomatology and may predict higher levels of depression and poorer quality of life in breast cancer patients over time [18,29,30]. Treatments that have successfully alleviated intrusive symptoms have incorporated behavioral techniques, relaxation, cognitive restructuring, and coping skills training [31,32]. However, most intervention studies have targeted intrusive symptoms in patients undergoing cancer treatments or after treatment [32]. Prior studies have not addressed intrusive thoughts in the period immediately following diagnosis, the point at which cancer-related distress may be at its peak. Our results suggest that by reducing these symptoms during this timeframe, beta-blockers may also reduce the likelihood of longer-term cancer-related intrusive thoughts.

Beta-blockers may have other benefits for cancer patients. Increasing evidence suggests that catecholamines accelerate tumor cell growth by stimulating angiogenesis, a first step in malignant transformation whereby additional vascular networks are recruited to the site of the primary tumor [33,34]. However, several recent studies have documented the restrictive action of beta-blockers, especially propranolol, in inhibiting the effects of catecholamines on cancer progression [35–37]. Researchers are now interested in beta-blockers' potential therapeutic value. Beta-blockers may increase cancer survival by possibly reducing metastatic spread [38].

Intrusive symptoms prolong stress-induced physiological activation [39]. Intrusive memories of a trauma reflect a highly vigilant cognitive state, which results in heightened physiological arousal as the body prepares for action. For some cancers, there is evidence that stress-related physiological activation might enhance tumor growth and metastases [40]. Thus, the findings from this study suggest a possible tool by which to target stress-induced physiological activation in newly diagnosed cancer patients. Beta-blockers may lessen the distressing intrusions that help maintain maladaptive physiological arousal.

Study limitations include nonrandomized beta-blocker use. However, our findings are fully in accord with other recent observational evidence from cardiac surgery that documented beta-blockade reduction of more serious post-traumatic symptomatology [8]. Because of our cross-sectional design, we cannot say with certainty that beta-blocker usage reduces intrusive thoughts, or vice versa. It is certainly possible that people who have more intrusive thoughts are more likely to take beta-blockers for other unrelated medical reasons. Nevertheless, these data serve as important preliminary evidence that beta-blocker usage may reduce intrusive thoughts in cancer patients, an important finding that should be further investigated experimentally.

This sample comprised exclusively of women. Although we do not have data on men, other studies have found that intrusions are stronger in women than men [41]. Furthermore, the cardiac surgery study found that beta-blockers reduced the strength of newly acquired emotional memories for women but not for men [8]. Finally, it should be noted that this study assessed the effect of beta-blockers on intrusive symptoms but not syndromal PTSD; future research should clarify the impact of beta-blockers on PTSD development.

Lipid-soluble beta-blockers have central nervous system effects and may impair emotional memory more strongly than the water-soluble agents, which have mainly peripheral effects [8]. In this study, only a small number of women used lipid-soluble beta-blockers; thus, our data may not fully represent pharmacokinetic-driven differences in cancer-specific intrusions. The potential risks of beta-blocker use include the medication's contribution to diabetes [42], weight-gain [43], and depressive symptoms [44]. However, our data revealed that beta-blocker use remained a significant predictor of fewer intrusions even after controlling for concurrent depression. Indications for beta-blockers can include cardiovascular disease and heart arrhythmias, migraines, and social or other anxiety



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disorders [45–48]. However, to our knowledge, participants in this study had been prescribed beta-blockers for hypertension. Nevertheless, the use of beta-blockers could be confounded by their indication and other variables not measured may have influenced their intended use.

Emotional arousal after a severe life stressor prolongs adrenergic activation [5]. Emotionally distressing intrusive thoughts occur frequently after a diagnosis of cancer [4]. Prolonged adrenergic activation increases risk for further post-traumatic intrusions and other related psychological distress over time [5,8]. Beta-blockers block adrenergic activation, and our findings suggest that beta-blockers may reduce intrusive symptoms in newly diagnosed cancer patients. This study provides a promising direction for future investigations on the pharmacological benefits of beta-blockers for cancer-related distress.

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## Conflict of interest

The authors declare that they have no conflicts of interest.

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