

## An open-label, fixed-dose study of bupropion effect on sexual function scores in women treated for breast cancer

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**Background:** Sexual morbidity after chemotherapy and hormonal therapy for breast cancer can seriously affect patients' quality of life. Bupropion is an antidepressant that has been reported to increase libido.

**Objective:** To investigate the improvement of sexual function in female breast cancer patients using bupropion.

**Patients and methods:** We performed an 8-week open trial using bupropion in women diagnosed with breast cancer who had received chemotherapy and were currently receiving adjunctive hormonal therapy. The Arizona Sexual Experience Scale (ASEX) was used. The ASEX scale includes five questions that evaluate sexual function in the following areas: libido, excitability and ability to reach orgasm. Women received oral Bupropion 150 mg/daily for 8 weeks and were evaluated prior to the initiation of the study and again during Weeks 4 and 8.

**Results:** Twenty patients were included in the study. At the beginning of the study, the mean ASEX score was 23.45 [21.67–25.24] 95% CI. After 4 weeks of treatment, we observed a reduction in the mean ASEX score that persisted until the end of the study, at eight weeks: 18.45 [16.59–20.31] 95% CI ( $P = 0.0003$ ) and 18.95 [16.60–21.30] 95% CI ( $P = 0.0024$ ), respectively.

**Conclusion:** In this non-controlled open trial bupropion 150 mg/daily was associated with improved sexual function in women receiving adjuvant systemic treatment for breast cancer.

**Key words:** antineoplastic agents, breast neoplasms, bupropion, libido, sexual behavior, hormonal therapy

### introduction

Breast cancer, the most common cancer in women, will affect approximately one in eight women in her lifetime [1]. Early diagnosis of breast cancer and advances in therapy have provided prolonged survival and high cure rates but there are few studies evaluating long term quality of life in this population [1]. Most women diagnosed with breast cancer will receive adjuvant systemic therapy including chemotherapy and hormonal therapy since the combination is superior to each isolated treatment modality [2]. Sexual morbidity after chemotherapy is an important problem that can negatively influence a patient's quality of life [3–5]. Steginga et al. [6] evaluated women post-breast cancer diagnosis and found that, if psychological changes are seen, changes in sexual activity and libido tend to be present as well.

A cancer diagnosis, like other chronic illness, affects the patient in multiple dimensions: psychological, functional,

social, physical and sexual. Recent reviews report the prevalence rates for sexual dysfunction range from 15% for physiological arousal difficulties to 64% for reduced desire [7–8].

Breasts are cultural symbols of femininity and sensuality. After breast cancer diagnosis perceptions femininity and sensuality can be affected by the various treatments including surgery, chemotherapy and hormonal therapy with subsequent effects on quality of life. In a study with women treated with radical mastectomy and systemic therapy, 25% showed various levels of depression and sexual problems [9].

There are studies showing that a crucial factor to predict sexual dysfunction in women diagnosed with breast cancer is adjuvant chemotherapy treatment. The literature demonstrates clear evidences that adjuvant chemotherapy is associated with an increase in sexual dysfunction incidence after mastectomy [10].

Bupropion is an antidepressant that belongs to the aminoketone class, and is not related to tricyclics or to serotonin reuptake inhibitors. Bupropion, unlike other antidepressants that negatively influence sexual function [11], seems to increase libido [12–13] and is generally well tolerated [14]. Side

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effects include difficulties with concentration, insomnia and tremors [15].

The mechanism by which bupropion has prosexual effects is unknown. Bupropion has effects on both dopamine and norepinephrine reuptake [16] and increased activity in both systems has been reported to be correlated with increased sexual responsiveness including orgasmic capacity [17]. Another speculated mechanism is an increase in adrenal androgens (dehydroepiandrosterone) or a decrease of serum prolactin [18].

Based upon the positive effects of bupropion on libido [19], an open trial was carried on to evaluate the relationship between this agent and sexual function in female breast cancer patients with sexual dysfunction while on adjuvant hormonal therapy and following completion of adjuvant chemotherapy.

## methods

This is an interventional non-controlled prospective study that enrolled 20 women with diagnosis of breast cancer who were previously treated with adjuvant chemotherapy and were on hormonal therapy. The study was approved by the local ethics committee. Signed informed consent was obtained from all patients prior to entering the study.

Inclusion criteria included sexually active women who had completed adjuvant chemotherapy and were on hormonal therapy (tamoxifen or aromatase inhibitor) and who had high scores measured by The Arizona Sexual Experience Scale (ASEX) [20]. The study was performed at Núcleo de Oncologia da Bahia, a private reference Cancer Center in the northeast of Brazil.

Data collection included social demographic variables (age, marital status, race, instruction and cancer staging) and three questionnaires: ASEX [20] is a scale that includes five topics related to sexual function evaluation – sex drive, sexual arousal, vaginal wetness, orgasm and sexual satisfaction.

Each topic is scored on a range from 1 (normal) to 6 (completely absent). Total scores ranges from 5 to 30 and higher scores correlate with greater sexual dysfunction. This scale has been validated for the Portuguese language [21] and the cutoff point for sexual dysfunction was 19, consistent with the cutoff point found in the original English scale [20].

Beck's Depression Inventory (BDI) [22] was used to evaluate depression status by a questionnaire with 21 topics each one with four choices ranging from 0 to 3 addressing personal feelings such as sadness, guilt, suicidal ideas and attitudes during the last week. Higher scores means higher degree of depression. In this study we used a Brazilian-validated version [23].

European Organization for Research and Treatment of Cancer (EORTC Q30) quality of life measurement scale was used to evaluate quality of life. It is a questionnaire with 36 items measuring functional states, psychological distress, fatigue and malaise, nausea and vomiting and other physical symptoms as well as social interaction and global quality of life. Each item has score ranged from 1 to 5. For the five functioning scales and the global quality of life a higher score means a better quality of life. For the symptoms items a higher score represents a worse quality of life [24]. This instrument was also previously validated in Portuguese [25].

Patients had to answer all three questionnaires during the first interview, prior of the initiation of Bupropion (150 mg, orally, daily in the morning). Subsequent evaluations were performed at weeks four and eight and included ASEX, BDI and EORTC Q30 questionnaires. The total period of bupropion intake was 56 days. Patients were followed during the whole period of the study. During the interviews, in addition to filling out the

questionnaires, patients received clinical evaluation and physical examination. Side effects were graded and reported to the ethics committee when present.

Data were analyzed using Stata software [26]. Initially, descriptive statistics were calculated for all variables in the study. After analyzing the variables, the Student's *t*-test for paired samples was chosen in order to compare the mean scores of sexual dysfunction and depression, in all three time-points, two-by-two. As far as the quality of life scores, the Wilcoxon test of signs was chosen with the same objective previously mentioned. Once patients were classified as having sexual dysfunction according to the criteria previously established, the McNemar test was employed, with a similar objective mentioned above but considering changes in the proportion of significance for paired samples. Categorical characteristics were analyzed by using Pearson's chi-square test. Statistical difference was considered when  $P < 0.05$ . The null hypothesis was that there would be no difference between the second and first scores of ASEX, denominated and third and first scores of ASEX.

## results

Patients' mean age was 49 years, 50% were Caucasian and 50% were afrodescendent. Most of the women (83%) were married and half had a graduate degree (50%). Cancer staging included 50% of stage I and 50% of stage II (Table 1).

ASEX scale results showed a significant decrease in total scores both in the 2nd and 3rd interviews (weeks four and eight respectively) compared with baseline. Total mean values at baseline, week four and week eight were 23.45; 18.45 and 18.95.

Using the Student's *t*-test for paired samples, an analysis was performed evaluating the mean score obtained for ASEX at week four minus the mean score obtained at baseline, thereafter denominated [score 2–1]; the mean score obtained at week eight minus the mean score obtained at baseline, thereafter denominated [score 3–1] and finally the mean score obtained in week eight minus the mean score obtained in week four, thereafter denominated [score 3–2]. The results obtained are depicted in Table 2. There was a statistically significant difference between the mean score obtained at week four and mean score obtained at baseline ( $P = 0.0003$ ) and between the

**Table 1.** Demographic characterization

Age (years)	50.6 ± 2.7
Race	
Caucasian	50.0%
Afro-descendent	50.0%
Marital status	
Single with a partner	–
Married	83.3%
Divorced	16.7%
Instruction (years of study)	
Less than 8 years	30.0%
More than 8 years	20.0%
Graduated	50.0%
Staging	
I	50.0%
II	50.0%

mean score obtained at week eight and mean score obtained at baseline ( $P = 0.0024$ ). Improvement was observed in total sexual function and in all five sexual areas at week four: sex drive, sexual arousal, vagina wetness, orgasm and sexual satisfaction; these findings persisted at week eight with the exception of sexual satisfaction that didn't reach statistical significance as can be seen in Table 3.

A similar analysis was performed for the BDI and EORTC Q30 scales as can be observed in Table 4. There was a significant difference found in the BDI at weeks four and eight ( $P = 0.038$ ) and ( $P = 0.022$ ) respectively. There was no significant difference on measured quality of life during the whole period of the study despite improvement in sexual function.

There was no correlation between ASEX scale improvement and better performance at EORTC Q30. On the other hand, at the end of the study (eight weeks) there was a positive correlation between BDI and ASEX scales ( $r = 0.494$ ,  $P = 0.027$ ): patients with lower BDI scores also showed lower ASEX scale total values.

## discussion

There is evidence of a high prevalence of sexual disturbances in women who have completed chemotherapy for breast cancer and who were on hormonal therapy [2–4]. The data presented in this small non-controlled open trial suggest that bupropion may improve sexual function in women with breast cancer experiencing sexual dysfunction on adjuvant hormonal therapy after completion of adjuvant chemotherapy. There was a significant improvement in total sexual function in all five sexual areas measured by the ASEX scale: sex drive, sexual arousal, vagina wetness, orgasm and sexual satisfaction, supporting the hypothesis that bupropion has prosexual effects on many aspects of sexual function [28]. Both measures of orgasm and libido showed improvement with better results in libido, in accordance with recent findings in a study that used bupropion in premenopausal women [28].

No major side effects were found in this study requiring interruption of therapy, suggesting bupropion as a safe drug

**Table 2.** Comparison between mean differences of ASEX scores

Variable	Mean	Standard deviation	P value
Score 2–1	–5.00	5.01	0.0003
Score 3–1	–4.50	5.76	0.0024
Score 3–2	0.50	3.35	0.51
Score 2–1:	Mean score obtained at week four minus the mean score obtained at baseline		
Score 3–1:	Mean score obtained at week eight minus the mean score obtained at baseline		
Score 3–2:	Mean score obtained at week eight minus the mean score obtained in week four		

**Table 3.** Mean (SD) values of ASEX scale\*

	First interview	Second interview	Third interview
How strong is your sex drive?	5.25 (0.71)	3.55 <sup>a</sup> (1.46)	3.75 <sup>b</sup> (1.51)
How easily are you sexually aroused (turned on)?	4.85 (0.81)	3.95 <sup>a</sup> (0.82)	4.00 <sup>b</sup> (1.07)
How easily does your vagina become moist or wet during sex?	4.55 (1.05)	3.90 <sup>a</sup> (1.16)	3.80 <sup>b</sup> (0.83)
How easily can you reach an orgasm?	4.75 (0.91)	4.10 <sup>a</sup> (0.78)	3.90 <sup>b</sup> (1.21)
Are your orgasms satisfying?	4.05 (1.50)	2.95 <sup>a</sup> (0.94)	3.50 (1.31)
Total	23.45 (3.81)	18.45 <sup>a</sup> (3.96)	18.95 <sup>b</sup> (5.02)

<sup>a</sup> $P < 0.05$  between first and second interview.

<sup>b</sup> $P < 0.05$  between first and third interview.

**Table 4.** Comparison between mean differences of BDI and EORTC scores

Variable	Mean	Standard deviation	P value	
Score 2–1	–2.70	5.41	0.037	
BDI	Score 3–1	–3.05	5.48	0.022
Score 3–2	–0.35	3.86	0.689	
Score 2–1	2.90	14.03	0.185	
EORTC	Score 3–1	4.30	10.52	0.067
Score 3–2	1.40	12.83	0.422	
Score 2–1:	Mean score obtained at week four minus the mean score obtained at baseline			
Score 3–1:	Mean score obtained at week eight minus the mean score obtained at baseline			
Score 3–2:	Mean score obtained at week eight minus the mean score obtained in week four			

to be used in this population. There was only one case of insomnia and another one of dry mouth in our population. No drug interactions between tamoxifen or aromatase inhibitors were noted.

In this study, bupropion was used for 8 weeks in accordance with previous studies [29–31]. The prosexual effect was observed after two weeks of treatment in the above mentioned studies even with doses as low as 75 mg/daily justifying the first evaluation at week four.

Although we observed a statistically significant decrease in the BDI score at weeks four and eight, the clinical relevance of these findings is uncertain since none of the subjects met the criteria for depression at baseline [22].

The EORTC quality of life scale is intended to measure the person's subjective sense of well-being derived from current experience of life as a whole [21].

Those areas of life or domains most important to an individual will thus have the most influence on quality of life. Sexual function is only one specific area analyzed by this extensive instrument so it was not expected that bupropion would significantly improve the means in the EORTC scale over time. Although we found no difference on quality of life during the whole period of the study, it is possible that with a larger number of subjects statistical significance could be achieved.

This is an exploratory observational study evaluating the effects of bupropion on breast cancer patients with sexual dysfunction and, therefore, no sample size calculation was performed. The design limitations of this study warrant caution in interpreting the results. First, since this was an open single-arm study, we cannot control to what extent the findings represent placebo effect. Second, the study includes a small number of subjects and may not be generalizable to all patients receiving adjuvant therapy for breast cancer. A third limitation of the study was the lack of investigation of a possible dose effect mentioned in a previous study [31] since the dose was maintained throughout the period in all subjects.

Besides sexual dysfunction, bupropion has also been evaluated for treatment of fatigue and depression in oncologic patients and their caregivers [31], suggesting that this drug might have an important role in the multidisciplinary approach of this complex patient population.

The findings presented here, suggest that oral bupropion 150 mg daily may improve sexual function in women with breast cancer but the possibility that the changes seen are a consequence of time since successful chemotherapy, the positive attitude with knowing their cancer is responding to treatment, comfort with the doctor asking questions about their sex life and is worth studying in a larger double-blind, placebo-controlled study in cancer survivors with sexual dysfunction.

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