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## The Impact of Mirtazapine Treatment on Patients with Breast Cancer in Sharkia Governorate

Eman Ali <sup>1</sup>, Hayam Elgohary <sup>1</sup>, Eman Elsebai <sup>2</sup>, Fatima M Sherif <sup>1</sup>, Dina Ali Abo Bakira\*<sup>1</sup>, Dalia H. Ibrahim <sup>1</sup><sup>1</sup> Psychiatry Department, Faculty of medicine, Zagazig university, Zagazig, Egypt<sup>2</sup> Medical Oncology Department, Faculty of Medicine, Zagazig university, Egypt

### Corresponding Author

Dina Ali Abo Bakira

Email address:

[Yasser.dina3042018@gmail.com](mailto:Yasser.dina3042018@gmail.com)

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### ABSTRACT

**Background:** Depressive symptoms are expected consequences following a diagnosis of breast cancer and have a detrimental effect on the prognosis of the disease. **Aim:** This study aimed to detect the benefits of adding the antidepressant drugs to the usual supportive psychotherapy provided by the oncology team to depressed breast cancer patients.

**Methods:** 400 breast cancer patients were screened for depression to reach the sample size (130) of depressed cancer patients, they were assessed for the presence of depression using SCID-I. Then, 130 depressed patients who had breast cancer were randomly categorized into two groups; Group I (65) received both of antidepressant medication (Mirtazapine) and usual supportive psychotherapy by the oncology team, while the other group; Group II (65) were subjected to the usual supportive psychotherapy alone with three months follow up. Diagnostic and Statistical Manual of Mental Disorders, (DSM-IV, SCID-I): was used to confirm a diagnosis of major depressive disorder. Initial assessment and after three months the two groups were reassessed specifically at the Hospital Anxiety and Depression Scale (HADS), as well as the scale for quality of life (WHOQOL-BREF).

**Results:** Statistically significant difference ( $p$ -value = 0.021, 0.032) between studied groups (group I and group II) as regard depression and anxiety domains of HADS respectively, as well as the (WHOQOL). Also a statistically significant association was revealed between depression severity and anxiety severity with total mastectomy ( $p=0.001$ ,  $p<0.001$  respectively).

**Conclusion:** Adding the antidepressant drugs to the usual supportive psychotherapy provided by the oncology team have better improvement of depressed breast cancer patients than using psychotherapy alone, as well as improve their quality of life.

**Keywords:** Depression; Breast Cancer; Mirtazapine; Sharkia Governorate.

### INTRODUCTION

Health systems around the world are facing a major challenge from cancer. Cancer of the breast affects one in eight women and is the second most frequent form of the disease worldwide. Breast cancer accounts for 6.5% of all cancer-related deaths globally in 2018, according to data compiled by the World Health Organization. It accounts for 18.9 percent of all cancer cases in

Egypt, and it is by far the most common kind of cancer among Egyptian women (35.1 percent among females and 2.2 percent among males) [1].

Due to its high mortality rate, effects on one's self-perception and sexual relationships, breast cancer is widely regarded as a terrible disease. Research shows that breast cancer patients have a significantly higher rate of psychological distress

and are at greater risk for developing major depression and anxiety [2].

Major depressive symptoms are common in breast cancer patients, although they are sometimes overlooked in treatment. This may be because oncologists are unfamiliar with screening for these symptoms or because patients with breast cancer are often unwilling to discuss any changes in their mood or feelings [3].

The negative effects of depression and its symptoms on quality of life, adherence to medical therapies, and even longevity make it crucial to accurately diagnose this condition [4]. Importantly, with the shift from the traditional system of management to a biopsychosocial medical network, the involvement of psychological aspects in the genesis and prognosis of breast cancer has received a great deal more attention [5].

In addition, breast cancer's reaction to mental illness may be different from that of other malignancies because it is a hormone-dependent neoplasm. Several research have looked at the link between depression treatment and longer life expectancy [6].

It is possible that psychological factors have a significant role in enhancing the response to the adjuvant therapy and several methods have been explored to lessen cancer patients' emotional suffering. Promoting the use of psychotherapy in the treatment of cancer is one such strategy. In addition, antidepressants could be important in resolving this issue [7,8].

This study aimed to detect the benefits of adding the antidepressant drugs to the usual supportive psychotherapy provided by the oncology team to depressed breast cancer patients in Sharkia Governorate.

**METHODS**

This cohort study was carried out on 130 breast cancer patients at oncology (outpatient clinic and the inpatient ward) and psychiatry departments in Sharkia Governorate, Egypt. They were collected from screening of 400 cancer patients for depression. This sample had been enrolled during the period from November 2021 till February 2022 then after 3-months period of follow up the participants were reassessed after 3 months.

**Sample size:**

According to CI 95% and Power of the test 80% and ratio of sample size 1: 1 and improvement

response in cancer breast patient treated with antidepressants drug about 45%. And assuming that without treatment, the ratio was 20%, so, the sample size was 130 patients (65 patients in each group. (Group 1) depressed patient treated with antidepressant (Mirtazapine) and (Group II) depressed patient treated with the usual supportive psychotherapy alone). The sample was selected from 400 breast cancer patients attended the outpatient clinic of Zagazig university hospitals. Participants were initially screened using the inclusion and exclusion criteria to determine study participation (Figure 1).

Cases with the following criteria were included; patients meet DSM-IV criteria for major depressive disorder according to El Missiry et al. [9], ages are between (18-60) years old in both sexes, breast cancer patients after surgery (modified radical mastectomy and total mastectomy surgery), and patients with no history of previous chemotherapy for breast cancer any time prior to study.

Cases with the following characteristics were excluded; age of patients <18 or >60 years, patients who were taking any antidepressant medication within 6 months prior to study, Patients with advanced stage of breast cancer, patients with psychotic disorders or mental retardation, and patients who were unwillingness or couldn't to comply with the assessment.

The following assessment procedures were performed on all patients under the constant surveillance of the supervisors:

**Semi-structured questionnaire:**

For collecting clinical and socio demographic data (duration since diagnosis, duration since surgery and the type of surgery, post-surgical health status, associated medical or psychiatric conditions).

**Diagnostic and Statistical Manual of Mental Disorders, (DSM-IV, SCID-I):**

Were used to confirm a diagnosis of major depressive disorder during the semi-structured interview, which included a full psychiatric sheet designed to facilitate accurate psychiatric diagnosis in adults. The SCID-I utilized in this research was validated and translated into Arabic by El Missiry et al. [9] at the Psychiatry department, Ain Shams University.

Psychometric assessment: All individuals diagnosed with major depressive disorder were subjected to:

***Hospital Anxiety and Depression Scale (HADS):***

In order to diagnose both with anxiety and depression. It's a self-report scale with 14 questions that has been proven effective in identifying depressive and anxious moods in the context of a hospital's outpatient medical clinic [10]. It has two 7-item measures, one for anxiety and one for depression, each having a score range of 0 to 21, and only takes 2–5 min to complete. The scale does not include items associated with symptoms that may have a physical cause (for example, insomnia and weight loss). As a result, the HADS is thought to be unbiased by concurrent general medical conditions.

Depressed patients were divided into two matched groups; one receives both of antidepressant drugs and usual supportive psychotherapy by the oncology team, while the other group will be subjected to the usual supportive psychotherapy alone.

***Quality of life (WHOQOL) scale:***

To evaluate the patients' emotional, spiritual, and social health. It is composed of 26 items in four categories. Mobility, daily activities, functional ability, energy, pain, and sleep are of the seven indicators of physical health. Image of oneself, negative thoughts, positive attitudes, self-esteem, learning capacity, memory concentration, religious, and mental state are all components of psychological wellness. There are three questions pertaining to interpersonal connections, social networks, and sexual activity. Money, security, health and social care, the built environment, educational possibilities, leisure time, noise and air pollution, and transportation are only few of the eight categories that make up environmental health. Measures of quality of life and overall health were included. The answer scale for the WHOQOL-BREF was a mandated five-point ordinal scale, with responses ranging from 1 to 5. The results were then linearly translated to a 0-100 scale [11,12].

After three months the two groups were reassessed specifically at the Hospital Anxiety and Depression Scale (HADS), as well as the scale for quality of life (WHOQOL-BREF).

Adherence was measured using Morisky test [13], nausea and vomiting severity were assessed by

grading score from zero to 3 in which zero means no nausea [14].

***Approvals:***

Participants were given thorough explanations of the study's goal and anticipated advantages. The entire project was conducted with the highest ethical consideration. Written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The Institutional Review Board number is (IRB): 6994

**STATISCAL ANALYSIS**

SPSS 27.0 (SPSS Inc., Chicago, IL, USA) was used for the data analysis [19]. Quantitative data were described using the mean, standard deviation, and range; qualitative data were expressed using numbers and percentages. The t-test was used to compare two sets of data where one set had a normal distribution to the other. Two sets of non-normally distributed variables were compared using the Mann-Whitney test. The Pearson correlation coefficient was calculated to examine the relationship between the study's variables. When applicable, we used the Chi-square test or the Fisher exact test to compare percentages of categorical variables.

**RESULTS**

When comparing the demographics of the two groups (group I and group II), no statistically significant differences were identified. (Age, socioeconomic status, residence, menses, education level, working status, marital status and number of children) ( $p > 0.05$  for each) (Table 1). The prevalence of depression in our study was 32.5% (**Figure 1**).

**Table 2** showed statistically significant ( $p$ -value = 0.001) increased depression in patients with total mastectomy (median = 14, IQR = 11 – 18) when compared with patients with partial mastectomy (median = 11, IQR = 10 – 14). Highly statistical significant ( $p$ -value < 0.001) increased anxiety in patients with total mastectomy (median = 14, IQR = 10 – 17) when compared with patients with partial mastectomy (median = 10, IQR = 7.5 – 11).

**Table 3** showed highly statistical significant ( $p$ -value < 0.001) decreased depression in HADS after treatment (median = 7, IQR = 6 - 8) when compared with HADS before treatment (median = 12, IQR = 10 – 15) in group I patients .Highly statistical significant difference ( $p$ -value < 0.001) in severity of depression in HADS before and after

treatment in group I. Highly statistical significant (p-value < 0.001) decreased depression in HADS after treatment (median = 8, IQR = 6 - 10) when compared with depression in HADS before treatment (median = 11, IQR = 10 - 15) in group II patients. Highly statistical significant difference (p-value < 0.001) in severity of depression in HADS categories before and after treatment in group II.

**Table 4** showed highly statistical significant (p-value < 0.001) decreased anxiety in HADS after treatment (median = 6, IQR = 6 - 7) when compared with HADS before treatment (median = 10, IQR = 8 - 14) in group I patients. Highly statistical significant difference (p-value < 0.001) of severity of anxiety in HADS categories before and after treatment in group I. Highly statistical significant (p-value < 0.001) decreased anxiety in HADS after treatment (median = 7, IQR = 6 - 9) when compared with HADS before treatment (median = 10, IQR = 8 - 14) in group II patients. Highly statistical significant difference (p-value <

0.001) of anxiety severity in HADS categories before and after treatment in group II.

**Table 5** showed statistically significant (p-value = 0.004) decreased depression in group I (median = 7 IQR = 6 - 8) when compared with group II (median = 8, IQR = 6 - 10). Also, there is statistically significant difference (p-value = 0.021) between studied groups (group I and group II) as regard severity of depression.

**Table 6** showed statistically significant (p-value = 0.045) decreased anxiety in group I (median = 6, IQR = 6 - 7) when compared with group II (median = 7, IQR = 6 - 9). Also, there is statistically significant difference (p-value = 0.032) between studied groups (group I and group II) as regard severity of anxiety.

We found high statistically significant increased WHOQOL physical, psychological, social, and environmental scores in group I when compared with group II. (**Table 7**).

**Table (1):** Comparisons between studied groups as regard demographic data.

		Group I (N = 65)		Group II (N = 65)		Stat. test	P-value
Age (years)	Median (IQR)	49 (45 - 53)		50 (44 - 56)		MW = 1747.5	0.089 NS
SES	High	32	49.2%	26	40%	X <sup>2</sup> = 5.1	0.077 NS
	Moderate	18	27.7%	30	46.2%		
	Low	15	23.1%	9	13.8%		
Residence	Urban	31	47.7%	28	43.1%	X <sup>2</sup> = 0.27	0.597 NS
	Rural	34	52.3%	37	56.9%		
Menses	Pre-men	29	44.6%	30	46.2%	X <sup>2</sup> = 0.03	0.860 NS
	Post-men	36	55.4%	35	53.8%		
Education level	Illiterate	13	20%	14	21.5%	X <sup>2</sup> = 0.18	0.980 NS
	Primary	19	29.2%	19	29.2%		
	Secondary	14	21.5%	15	23.1%		
	University	19	29.2%	17	26.2%		
Work	Not working	27	41.5%	35	53.8%	X <sup>2</sup> = 1.97	0.160 NS
	Working	38	58.5%	30	46.2%		
Marital status	Single	22	33.8%	15	23.1%	X <sup>2</sup> = 2.9	0.230 NS
	Married	27	41.5%	26	40%		
	Divorced/ widow	16	24.6%	24	36.9%		
No. of children	Median (IQR)	3 (0 - 5)		3 (0 - 6)		MW = 1964	0.485 NS

S: p-value < 0.05 is considered -significant.

MW: Mann Whitney U test.

NS: p-value > 0.05 is considered non-significant

X<sup>2</sup>: Chi-square test.

**Table (2):** Correlation between mastectomy and severity of depression & anxiety (before treatment) in all studied patients.

		Mastectomy		MW	P-value
		Total (n = 41)	Partial (n = 89)		
Depression	Median	14	11	1191	0.001 S
	IQR	11 - 18	10 - 14		
Anxiety	Median	14	10	917	< 0.001 HS

	<b>IQR</b>	10 - 17	7.5 - 11		
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S: p-value < 0.05 is considered significant.

HS: p-value < 0.001 is considered highly significant.

MW: Mann Whitney U test.

**Table (3): Comparison of depression severity (HADS) before and after treatment in studied groups.**

Depression		Before (N = 65)		After (N = 65)		Stat. test	P-value
HADS (Group I)	Median (IQR)	12 (10 – 15)		7 (6 – 8)		MW = 258.5	< 0.001 HS
HADS categories (Group I)	Normal	0	0%	45	69.2%	X <sup>2</sup> = 78.6	< 0.001 HS
	Mild	20	30.8%	15	23.1%		
	Moderate	30	46.2%	5	7.7%		
	Severe	15	23.1%	0	0%		
HADS (Group II)	Median (IQR)	11 (10 – 15)		8 (6 – 10)		MW = 779.5	< 0.001 HS
HADS categories (Group II)	Normal	0	0%	29	44.6%	X <sup>2</sup> = 47.9	< 0.001 HS
	Mild	18	27.7%	21	32.3%		
	Moderate	34	52.3%	14	21.5%		
	Severe	13	20%	1	1.5%		

MW: Mann Whitney U test

HS: p-value < 0.001 is considered highly significant.

X<sup>2</sup>: Chi-square test.

**Table (4): Comparisons of anxiety severity (HADS) before and after treatment in studied groups.**

Anxiety		Before (N = 65)		After (N = 65)		Stat. test	P-value
HADS (group I)	Median (IQR)	10 (8 – 14)		6 (6 – 7)		MW = 556	< 0.001
HADS categories (Group I)	Normal	11	16.9%	50	76.9%	X <sup>2</sup> = 49.6	< 0.001 HS
	Mild	26	40%	10	15.4%		
	Moderate	17	26.2%	5	7.7%		
	Severe	11	16.9%	0	0%		
HADS (group II)	Median (IQR)	10 (8 – 14)		7 (6 – 9)		MW = 1049	< 0.001 HS
HADS categories (group II)	Normal	15	23.1%	37	56.9%	X <sup>2</sup> = 21.5	< 0.001 HS
	Mild	21	32.3%	14	21.5%		
	Moderate	19	29.2%	14	21.5%		
	Severe	10	15.4%	0	0%		

MW: Mann Whitney U test.

HS: p-value < 0.001 is considered highly significant.

X<sup>2</sup>: Chi-square test.

**Table (5) Comparisons between studied groups as regard depression severity (HADS).**

Depression		Group I (N = 65)		Group II (N = 65)		Stat. test	P-value
HADS (before)	Median (IQR)	12 (10 – 15)		11 (10 – 15)		MW = 2024.5	0.680 NS
Depression severity (before)	Mild	20	30.8%	18	27.7%	X <sup>2</sup> = 0.49	0.780 NS
	Moderate	30	46.2%	34	52.3%		
	Severe	15	23.1%	13	20%		
HADS (after)	Median (IQR)	7 (6 – 8)		8 (6 – 10)		MW = 1503.5	0.004 S
Depression severity (after)	Normal	45	69.2%	29	44.6%	X <sup>2</sup> = 9.7	0.021 S
	Mild	15	23.1%	21	32.3%		
	Moderate	5	7.7%	14	21.5%		
	Severe	0	0%	1	1.5%		

MW: Mann Whitney U test.

HS: p-value < 0.001 is considered highly significant.

X<sup>2</sup>: Chi-square test.

Table (6): Comparisons between studied groups as regard severity of anxiety in (HADS).

Anxiety		Group I (N = 65)		Group II (N = 65)		Stat. test	P-value
HADS (before)	Median (IQR)	10 (8 – 14)		10 (8 – 14)		MW = 2065	0.824 NS
Anxiety severity (before)	Normal	11	16.9%	15	23.1%	X <sup>2</sup> = 1.3	0.728 NS
	Mild	26	40%	21	32.3%		
	Moderate	17	26.2%	19	29.2%		
	Severe	11	16.9%	10	15.4%		
HADS (after)	Median (IQR)	6 (6 – 7)		7 (6 – 9)		MW = 1690.5	0.045 S
Anxiety severity (after)	Normal	50	76.9%	37	56.9%	X <sup>2</sup> = 6.9	0.032 S
	Mild	10	15.4%	14	21.5%		
	Moderate	5	7.7%	14	21.5%		

MW: Mann Whitney U test.

S: p-value < 0.05 is considered significant.

X<sup>2</sup>: Chi-square test.

NS: p-value > 0.05 is considered non-significant.

Table (7) Comparisons between studied groups as regard WHOQOL.

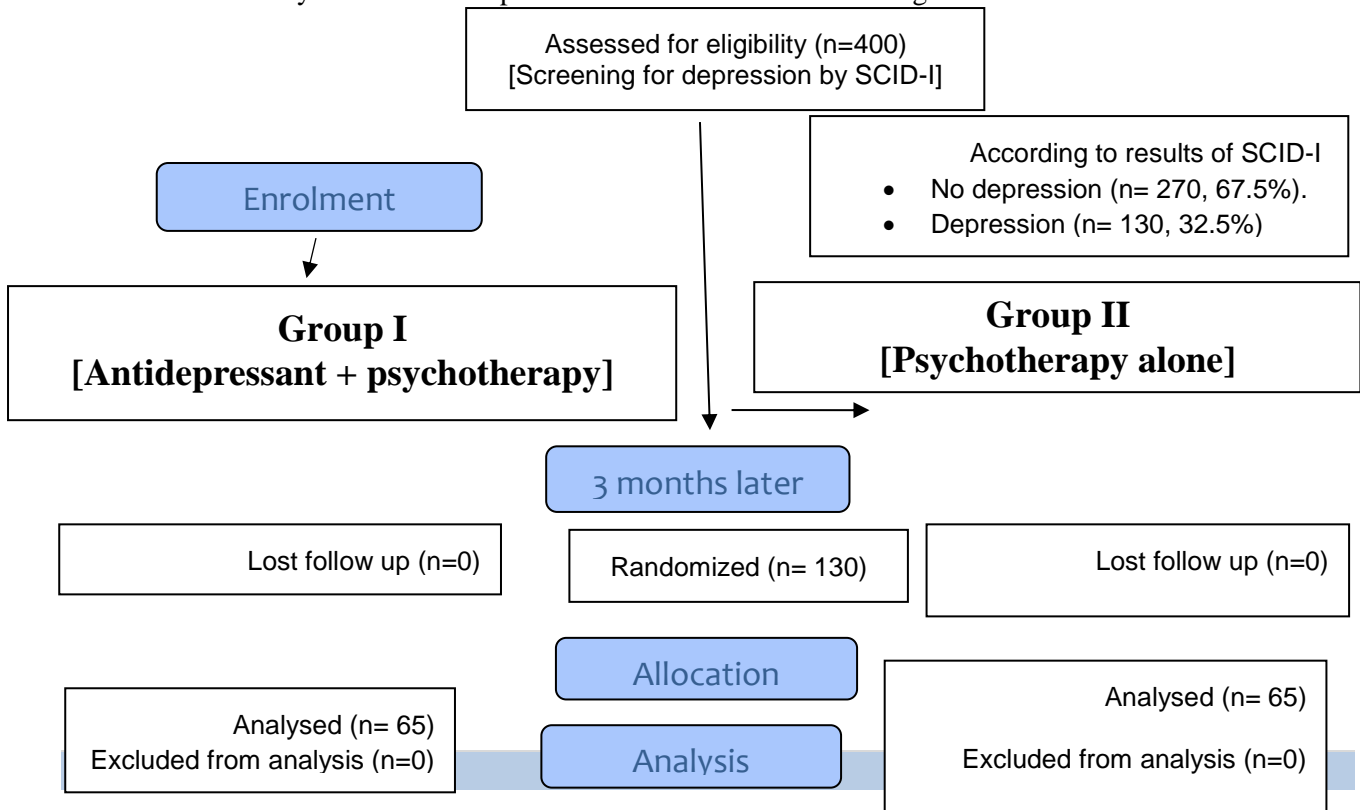
WHOQOL	Group I (N = 65)	Group II (N = 65)	MW	P-value
Physical (before)	36 (32 – 38)	35 (32 – 38)	2008.5	0.627 NS
Psychological (before)	32 (29 – 34)	32 (29 – 34)	2106.5	0.978 NS
Social (before)	40 (37 – 43)	41 (38 – 43)	1846	0.212 NS
Environmental (before)	45 (40 – 48)	44 (41 – 47)	1969.5	0.504 NS
Physical (after)	68 (64 - 70.5)	50 (48 – 54)	0.0	< 0.001 HS
Psychological (after)	74 (71 – 76)	49 (46 – 51)	0.0	< 0.001 HS
Social (after)	77 (74.5 – 80)	63 (61 - 66.5)	0.0	< 0.001 HS
Environmental (after)	78 (76 – 82)	63 (60 – 66)	0.0	< 0.001 HS

WHOQOL data was expressed as median (IQR)

HS: p-value < 0.001 is considered highly significant.

MW: Mann Whitney U test.

NS: p-value > 0.05 is considered non-significant.



**Figure (1):** Consort flow diagram showing study design

**DISCUSSION**

Postoperative depression affects 20–45 percent of breast cancer patients. Mental anguish, anxiety, and affective disorders are common co-occurring conditions in women with breast cancer. After being diagnosed with breast cancer, many people feel overwhelmed emotionally, physically, and socially [15].

In the current study, patients mean age was 46.69 ± 7.30 years in group 1 and 47.26 ± 7.97 years in group II. In line with our findings, Ng et al. [16] revealed that patients aged 41–60 made up the largest age group, followed by those aged 20–40.

Neither group differed much from the other in terms of education, with roughly the same percentage of participants at each level of education. Illiterate participants represented 20% and 21.5% in group I and group II respectively.

The prevalence of depression in our study was 32.5%. Our finding was in line with the finding reported by Allam et al. [17] who found that major depressive disorder was found in 42.5% of the women with breast cancer who were evaluated, and anxiety was present in 15% to 25%. Anxiety and depression were reported to be slightly more common in our study than in a study by Hassan et al. [18], who found prevalence rates of 31.7% and 22.0%, respectively. Anxiety, depression, and perceived stress symptoms were all somewhat common, but not nearly as common as Alagizy et al. [19] had observed (73.3 %m 68.7 %, and 78.2 percent respectively) and 31.25 percent of the study population experienced a dual diagnosis of anxiety and depression.

No previous studies to the best of our knowledge have compared the effectiveness of combination between antidepressants and psychotherapy in treatment of depression in breast cancer versus the psychotherapy alone. However, some studies have revealed the value of treatment with each treatment modality separately or the antidepressant were used in both groups. Pre-therapeutic assessments revealed that cancer patients have high levels of anxiety and sadness throughout the course of their treatment. The (HADS) and (WHOQOL) results improved significantly following therapy in our study compared to pre-treatment values. Moreover,

the degree of improvement was higher in the combination group (p < 0.001 for each).

Regarding role of pharmacotherapy, in line with our results, Liu et al. [15] conducted a study on 303 people with breast cancer with mild to moderate depression. The researchers found that the Hamilton Rating Scale for Depression (HAM-D-17) ratings of those who had received either racemic ketamine or S-ketamine were significantly lower than those in the control group (P<0.05).

However, in contrast to our results Thirty-five female outpatients diagnosed with breast cancer and major depression or adjustment disorder with sad mood according to the DSM-III-R were participated in a 6-week study conducted by Musselman et al. [20]. Primary effectiveness was determined by the difference in score between baseline and posttreatment on Hamilton Rating Scale for Depression (HAM-D), and secondary effectiveness was determined by the difference in score between baseline and posttreatment on the Clinical Global Impressions-Severity of Illness scale (CGI-S). They discovered no statistically significant difference between the paroxetine and desipramine groups and the placebo group in the mean change in overall HAM-D and CGI-S scores from baseline to 6-week endpoint Symptom improvement on the depressed, anxious, cognitive, neuro-vegetative, and somatic components of the HAM-D and the Hamilton Rating Scale for Anxiety was likewise comparable between groups. This difference may be contributed to the difference in study design, inclusion criteria and antidepressant drugs used.

Regarding role of psychotherapy, The purpose of the study by Karulkar. [21] was to determine whether or not cancer patients experience anxiety and depression, and if so, whether or not supportive therapy can alleviate these symptoms. The researchers found that the average pre-therapy anxiety score was 11.92 (±1.63), and the average pre-therapy depression score was 19.78 (±1.76), indicating the presence of anxiety and depression in cancer patients. Furthermore, Interpersonal psychotherapy (IPT), problem-solving therapy (PST), and brief supportive psychotherapy (BSP) were compared in a randomised controlled trial by Blanco et al. [22]. (BSP). They demonstrated that IPT, PST, and BSP were linked to substantial

enhancements in a variety of depression and quality of life measures.

Supportive-expressive group therapy did not substantially alleviate anxiety and depression compared to the control group in a randomised controlled study of supportive-expressive group therapy and body-mind-spirit intervention for Chinese patients with non-metastatic breast cancer conducted by Ho et al. [23]. The discrepancy between studies may be due to the difference in study populations.

In our study, there is a statistically significant improvement of both the domains of Hospital Anxiety and Depression Scale (HADS) after treatment as compared to the before treatment value. Moreover, the degree of improvement was higher in the combination group. This is similarly reported in results of Fann et al. [24] in their systematic review article that presented 14 studies in which antidepressants were prescribed for breast cancer patients accompanied by psychotherapy; in some trials the efficacy of selective serotonin reuptake inhibitors such as fluoxetine, paroxetine, and sertraline has been emphasized. In addition, the effectiveness of psychotherapy approaches on pain, fatigue, and distress reduction and improvement in depression and anxiety have been mentioned.

Regarding the role of combined pharmacotherapy and psychotherapy, Treatment with escitalopram (10-20 mg QD) and brief therapy improved global health and global quality of life in patients with non-metastatic breast, lung, and colon malignancies and major depressive disorder, according to research from Spain conducted by Rodríguez et al. [25]. Our results were also in line with Nikbakhsh et al. [26] who showed that Patients' quality of life improved noticeably after receiving combination therapy. Also, In line with our finding, the UK study by Hodges et al. [27] recommended a combination of pharmacotherapy and counseling in patients with breast cancer.

In our study, we found statistically significant association between anxiety and depression with total mastectomy, in line with our results, Lopes et al. [28] illustrated that women who submitted to total mastectomy experienced depression more frequently than those who had breast conserving surgery. These results are also in accordance with a recent meta-analysis by Padmalatha et al. [29]

Our study strength points: It conducted in a psychiatric clinic rather than a primary care clinic,

giving us access to the patient's good assessment, which was critical in confirming the diagnosis and collecting accurate data about the participants.

There are some limitations to the study; the first limitation is the cohort type of our study that lacked a control group. Second; the influence of cancer stage on depression was not evaluated since tumor staging was not performed on the study sample.

### Conclusion

Adding the antidepressant drugs to the usual supportive psychotherapy provided by the oncology team have better statistically significant improvement of depressed breast cancer patients, as well as improve their quality of life.

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