Effect of Reboxetine on Major Depressive Disorder in Breast Cancer Patients: An Open-Label Study

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Background: Depression is a common disorder in cancer patients, and it is associated with reduced quality of life, abnormal illness behavior, pain, and suicide risk. A few studies have investigated the effects of tricyclic antidepressants and serotonin reuptake inhibitors in cancer patients. No data are available regarding the use of reboxetine, a norepinephrine reuptake inhibitor that has been shown to be safe (e.g., absence of clinically significant drug-drug interactions and cytochrome P450 metabolism) and effective in the treatment of depressed patients, including those with medical illness (e.g., Parkinson's disease, human immunodeficiency virus infection).

Method: The effects of reboxetine were investigated in 20 breast cancer patients with a DSM-IV diagnosis of major depressive disorder in an open, prospective 8-week trial. Severity of depression was assessed with the 17-item Hamilton Rating Scale for Depression (HAM-D). Psychiatric symptoms (Brief Symptom Inventory [BSI]), styles of coping with cancer (Mini-Mental Adjustment to Cancer [Mini-MAC]), quality of life (European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire C30 [EORTC-QLQ-C30]), and Clinical Global Impressions scale scores were also monitored.

Results: At 8 weeks, a significant ($p < .01$) reduction was observed in HAM-D scores, several BSI dimension scores, and Mini-MAC hopelessness and anxious preoccupation scores. A significant ($p < .05$) improvement from baseline to endpoint was found on the EORTC-QLQ-C30 subfactors emotional, cognitive, dyspnea, sleep, and global. Discontinuation was necessary in 1 subject because of hypomanic switch and in another because of side effects (tachycardia, tension). Seven patients experienced transient side effects (e.g., mild anxiety, insomnia, sweating).

Conclusion: In this open trial, reboxetine appeared to be well tolerated and promising in reducing depressive symptoms and maladjusted coping styles and in improving scores on quality-of-life parameters.

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Depression represents a significant complication in patients with cancer. It has been reported that from 10% to 40% of cancer patients, in any phase of illness, can be diagnosed as having a depressive disorder, including major depressive disorder, adjustment disorder with depressed mood, or depression secondary to cancer itself or cancer medication (e.g., chemotherapeutic agents, corticosteroids).[1–4]

The importance of correct recognition and treatment of depression is linked to the remarkably negative consequences of depression for cancer patients and their families, including abnormal illness behavior,[5] high prevalence of pain,[6] reduced quality of life,[7] higher suicide risk,[8] and family emotional problems.[9]

Only a few studies, however, have investigated the effects of antidepressants in cancer patients who present with depressive disorders. In a pilot study of 12 cancer patients with mixed diagnoses (major depression, dysthymia, and adjustment disorders), Evans et al.[10] found significantly reduced depressive symptoms in patients treated with imipramine (150 mg/day) in comparison with a nontreated control group. The effect of mianserin was evaluated by Costa et al.[11] in a placebo-controlled study of 73 cancer patients with major depression. Response to treatment at 4 weeks was higher among mianserin-treated patients than placebo-treated patients (77% vs. 48.6%), while dropout was lower in those receiving mianserin. In comparison with that study, van Heeringen and Zivkov[12] showed that mianserin (30–60 mg/day) was superior to placebo in reducing depressive symptoms in breast cancer patients and that more placebo-treated patients prematurely terminated the study, due to lack of efficacy, than mianserin-treated patients (55% vs. 21%). Mianserin and placebo did not differ with regard to side effects in either study.

The most recent studies using selective antidepressants to treat depression in cancer patients have shown favorable results for these agents. In a 5-week randomized clinical trial carried out in 69 cancer patients with mixed psychiatric diagnoses (major depression and adjustment disorders), Razavi et al.[13] showed a higher reduction of psychological symptoms (e.g., anxiety, hostility, psychoticism) among fluoxetine-treated patients than placebo-treated patients. However, no difference was found between groups with regard to the total depression score, and the response rate (improvement of ≥ 50% on the Montgomery-Asberg Depression Rating Scale [MADRS]) was quite low and comparable in both groups (31% fluoxetine and 33% placebo). Dropout was also higher in the fluoxetine group (50%) than in the placebo group (17.9%).

Different results were obtained by Holland et al.[14] in a double-blind, 6-week study comparing fluoxetine and desipramine in 40 women with cancer of different sites and comorbid psychiatric diagnoses (major depression, adjustment disorder). Both drugs significantly improved anxiety, depression, and quality of life and were well tolerated, with no difference between fluoxetine and desipramine. In comparison with the Razavi et al.[13] study, discontinuation in fluoxetine-treated patients was lower (28.6%), while 41.2% of desipramine-treated patients dropped out. The use of fluoxetine was also recently tested by Fisch et al.[15] in a large survey evaluating depressive symptoms with a 2-item question in advanced cancer patients. The authors showed that, in comparison with placebo, fluoxetine (20 mg/day) significantly improved certain parameters of quality of life and the extent of depression.

In a study comparing a different tricyclic antidepressant (TCA), amitriptyline, and a different selective serotonin reuptake inhibitor (SSRI), paroxetine, Pezzella et al.[16] found that both drugs were effective in reducing depressive symptoms among breast cancer patients, but the prevalence of adverse side effects was high (59.6% and 53.4%, respectively). In a pilot open trial involving 20 terminally ill patients with cancer of different sites, Theobald et al.[17] showed that the noradrenergic and specific serotonergic antidepressant mirtazapine was effective in reducing depressive symptoms and in improving quality of life.

However, different clinical situations may indicate the need for different drug treatment among cancer patients with comorbid depressive disorders. For example, concomitant chemotherapy regimens can cause significant side effects (e.g., nausea and vomiting, reduction of appetite, oral mucositis), which may proscribe the use of TCAs[18] and limit the use of SSRIs.[19,20]

Among the third-generation antidepressants, reboxetine, a selective and specific norepinephrine reuptake inhibitor, has demonstrated superior efficacy to that of placebo and similar or greater efficacy to that of TCAs and SSRIs in several studies.[21–25] An open-label study of reboxetine in 16 patients with Parkinson's disease has shown its efficacy and low incidence of side effects in the treatment of depression.[26] In a more recent open-label study of 15 human immunodeficiency virus (HIV)–infected subjects with major depression who completed a 12-week trial with reboxetine, the authors found an improvement of ≥ 50% on the MADRS, with a low incidence of side effects (e.g., insomnia, sweating, shivering).[27] Some pharmacologic properties (e.g., absence of clinically significant pharmacodynamic or pharmacokinetic drug-drug interactions, safe cytochrome P450 profile) and clinical properties (e.g., energy-enhancing effect; reduction of psychomotor retardation, anxiety, and cognitive disturbance; safe profile at cardiovascular level)[28–31] can be further advantages in oncology, hypothetically counterbalancing the side effects of cancer treatment, especially, but not only, chemotherapy (e.g., fatigue, impairment of cognitive functions).

No data are available about the use of reboxetine among cancer patients. The aim of this open trial was to assess the effects of reboxetine in cancer patients with major depressive disorder.

METHOD

Sample

Subjects participating in this open trial were patients with cancer who attended the Outpatient C-L Psychiatry and Psycho-Oncology Service, S. Anna University Hospital, Ferrara, in northern Italy. Criteria for inclusion were age between 18 and 70 years, DSM-IV diagnosis of major depressive disorder, Karnofsky Performance Status[32] score of ≥ 80, and no psychotic symptoms. Reboxetine treatment was started at a dosage of 2 mg once a day, with increasing dosage according to clinical response to 10 mg per day. Written informed consent to treatment was obtained from all patients as required by the institutional review board of the hospital.

Procedure

Subjects participated in the study for 8 weeks, which included a baseline visit (T0), a visit at 2 weeks (T1), a visit at 4 weeks (T2), and a visit at 8 weeks (T3).

Assessment consisted of the 17-item Hamilton Rating Scale for Depression (HAM-D),[33] to rate depression (T0, T2, T3); the Brief Symptom Inventory (BSI),[34] to rate psychiatric symptoms (T0, T2, T3); the Mini-Mental Adjustment to Cancer Scale (Mini-MAC),[35] to assess coping with cancer (T0, T3); and the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire C30 (EORTC-QLQ-C30),[36] to rate quality of life (T0, T2, T3). Clinical improvement was also assessed using the Clinical Global Impressions scale (CGI)[37] (T1, T2, T3). Data were analyzed using SPSS

software (SPSS 10.0; SPSS Inc., Chicago, Ill). All tests were 2-tailed, with an alpha level of .05.

RESULTS

Of 25 women affected by breast cancer and eligible for the study, 22 (88%) agreed to participate. Mean ± SD age was 58 ± 7 years (range, 43–69 years), and mean time since diagnosis was 10.6 ± 8.7 months (range, 1–24 months). Most were married (N = 17, 77.3%), and half (N = 11, 50.0%) were retired. Education ranged from 5 to 18 years (mean ± SD = 11.1 ± 3.6 years). Stage of illness was local (N = 14, 63.8%), loco-regional (N = 3; 13.6%), or metastatic (N = 5; 22.7%). All patients had undergone surgical intervention, and 17 (77.2%) were receiving active treatment (chemotherapy and/or radiotherapy, hormone therapy) at the time of the study. Five patients had received prior treatment with other antidepressants (fluoxetine N = 2, sertraline N = 1, mianserin N = 1, trazodone N = 1), which was discontinued because of insufficient clinical response or side effects.

Mean ± SD reboxetine dose was 5 ± 2 mg (range, 4–10 mg). Twenty patients completed the study. At T1, reboxetine was discontinued because of hypomanic switch in a breast cancer patient with a family history of psychiatric disorders (a sister with a diagnosis of schizophrenia who had died of melanoma). Another breast cancer patient, who reported side effects at T1 (tachycardia, vertigo, insomnia, and intolerable anxiety and tension during the day), was not available at T2.

Depression and Self-Reported Psychiatric Symptoms

Mean HAM-D scores significantly decreased over the 8-week period of treatment (T0: 21.76 ± 3.89; T3: 11.61 ± 9.87; t = 4.27, p < .001) (Table 1). Fourteen patients (70%) showed clinical improvement as indicated by a reduction of ≥ 50% in the HAM-D baseline score, 4 patients showed a reduction in HAM-D score of less than 50%, and 2 patients did not respond to treatment (no change or worsening of depression).

Significant improvements were shown on all of the BSI subscales, specifically obsessive-compulsive (t = 3.89, p = < .01), depression (t = 5.07, p < .001), interpersonal sensitivity (t = 2.17, p = .03), anxiety (t = 6.34, p < .001), phobic anxiety (t = 3.13, p = .003), psychoticism (t = 4.32, p < .01), and paranoid ideation (t = 2.1, p = .042). Mean total BSI scores (global stress index) also showed a significant decrease between T0 (1.45 ± 0.41) and T3 (0.74 ± 0.59; t = 4.41, p < .001) (Table 1).

Coping and Quality of Life

Compared with T0, there were significant differences at T3 in the mean Mini-MAC scores hopelessness (25.42 ± 2.76 vs. 17.25 ± 6.38; t = 5.25, p < .001) and anxious preoccupation (28.38 ± 3.21 vs. 21.18 ± 6.31; t = 4.54, p < .01) (Table 1).

Mean scores on EORTC-QLQ-C30 subscales also changed significantly over time (Table 1). Significant improvements were demonstrated for some functioning scales, namely the emotional (T0: 12.90 ± 2.07; T3: 8.35 ± 3.01; t = 5.57, p < .001), cognitive (T0: 4.60 ± 1.46; T3: 3.42 ± 1.45; t = 2.56, p = .014), and global subscales (T0: 4.55 ± 1.46; T3: 9.07 ± 3.64; t = 5.15, p < .001). With regard to the symptom scales, significant differences were shown on dyspnea (T0: 1.65 ± 0.48; T3: 1.07 ± 0.26, t = 4.75, p < .01) and sleep (T0: 2.35 ± 0.48; T3: 1.50 ± 0.76, t = 4.22, p < .01).

Table 1. Effects of Reboxetine on HAM-D, BSI, Mini-MAC, and EORTC-QLQ-C30 Scores

	Baseline (T0)		Week 4 (T2)		Week 8 (T3)	
Measure	Mean	SD	Mean	SD	Mean	SD
HAM-D	21.76	3.89	12.06	7.41	11.61	9.87**
BSI						
Somatization	1.02	0.59	0.76	0.49	0.70	0.46
Obsessive-compulsive	1.64	0.68	0.97	0.79	0.72	0.81**
Depression	2.57	0.65	1.35	1.08	1.08	1.14**
Interpersonal sensitivity	1.23	0.63	0.88	0.58	0.81	0.59*
Anxiety	2.00	0.41	1.16	0.64	0.98	0.59**
Phobic anxiety	0.73	0.31	0.51	0.51	0.37	0.41**
Hostility	0.89	0.79	0.74	0.87	0.53	0.83
Paranoid ideation	1.15	0.76	0.71	0.62	0.67	0.68*
Psychoticism	1.54	0.58	0.80	0.81	0.62	0.78**
Global stress index	1.45	0.41	0.89	0.61	0.74	0.59**
Mini-MAC						
Fighting spirit	8.76	2.77			9.06	2.99
Hopelessness	25.42	2.76			17.25	6.38**
Fatalism	12.76	3.36			13.30	2.65
Anxious preoccupation	28.38	3.21			21.18	6.31**
Avoidance	11.00	2.96			11.50	3.14
EORTC-QLQ-C30						
Functioning scales						
Role	2.10	0.30	2.11	0.34	2.01	0.10
Emotional	12.90	2.07	9.23	2.68	8.35	3.01**
Social	3.30	0.92	3.05	0.89	3.42	1.39
Cognitive	4.60	1.46	3.64	1.65	3.42	1.45*
Physical	6.00	0.97	6.24	1.10	5.64	0.74
Global quality (reverse)	4.55	1.46	7.82	2.98	9.07	3.64**
Symptom scales						
Pain	2.70	0.92	3.05	1.39	3.01	1.69
Nausea, vomiting	2.70	1.03	2.35	0.70	2.30	0.67
Fatigue	6.88	1.36	6.23	1.09	6.01	1.56
Dyspnea	1.65	0.48	1.41	0.50	1.07	0.26**
Sleep	2.35	0.48	1.94	0.55	1.50	0.76**
Appetite loss	1.60	0.68	1.47	0.51	1.42	0.76
Constipation	1.10	0.30	1.00	0.10	1.14	0.36
Diarrhea	1.00	0.10	1.00	0.10	1.00	0.10
Financial	1.00	0.10	1.11	0.33	1.14	0.36

*p < .05.
**p < .01.
Abbreviations: BSI = Brief Symptom Inventory, EORTC-QLQ-C30 = European Organization for Research Treatment of Cancer Quality-of-Life Questionnaire C30, HAM-D = 17-item Hamilton Rating Scale for Depression, Mini-MAC = Mini-Mental Adjustment to Cancer Scale.

Efficacy and Tolerability

A significant reduction was observed in mean CGI-Severity of Illness score from T1 (3.82 ± 1.01) to T3 (2.88 ± 1.31; $t = -2.54$, $p = .01$). Likewise, scores on the CGI-Global Improvement changed significantly, with mean scores of 2.88 ± 0.60 at T1 and 2.35 ± 0.93 at T3 ($t = 2.14$, $p = .039$) and with most patients ($N = 14$, 70%) rated as very much/much improved. Except for 1 patient who dropped out at T1 because of increasing side effects (tachycardia, vertigo, insomnia, anxiety and tension during the day), reboxetine was well tolerated by most participants. Minor symptoms (i.e., slight agitation, slight and transient insomnia, sweating) were reported by 7 patients.

DISCUSSION

We investigated the effects of reboxetine in breast cancer patients with major depressive disorder for whom antidepressant treatment with other drugs (e.g., TCAs or SSRIs) was not possible, mainly because of the side effects of chemotherapy. Scores on observer-rated (HAM-D) and self-rated (BSI) psychiatric symptoms showed significant reductions from baseline to endpoint at 8 weeks. These results are in line with studies demonstrating the antidepressive effect of reboxetine both in psychiatric patients[21–25] and in patients with medical illness (e.g., Parkinson's disease, HIV infection).[26,27] These findings of efficacy are particularly interesting because, in the specific setting of oncology, the problem of major depressive disorder merits special attention.[1–4] In fact, on the one hand, it has been reported that only a minority of cancer patients showing symptoms of severe depression are recognized by physicians and receive adequate treatment.[38] On the other, as pointed out by several studies, depression may increase the risk of nonadherence to treatment,[39] abnormal illness behavior,[5] perception of pain,[6] suicide,[8] and request for assisted suicide and euthanasia.[40]

For these reasons and because of the paucity of clinical studies of antidepressant therapy in depressed cancer patients, Ballenger et al.[41] expressed their concern and indicated an urgent need for more investigation in the area. A recent proposal has been presented suggesting the use of algorithms to help oncologists in recognizing depression and treating identified depressed cancer patients according to their type of symptoms (e.g., depression with prominent fatigue, depression with insomnia).[42] An interesting further finding of our study was that treatment was associated with significant changes in measures of coping strategies. More specifically, the most dysfunctional cognitive and behavioral response to cancer, such as the tendency to adopt a pessimistic attitude about the illness (hopelessness) and to be persistently focused on and preoccupied by the illness (anxious preoccupation), improved after 8 weeks of treatment. This result is in line with other research indicating that, rather than fatalism, avoidance, and fighting spirit, hopelessness is a more important dysfunctional coping style. In fact, hopelessness has been shown to be associated with abnormal illness behavior,[5,43] suicide ideation,[44] and a higher risk of cancer relapse and mortality.[45]

A related suggestive result was that the patients' quality of life changed over the period of treatment. More specifically, the emotional and cognitive dimensions and the global level of the patients' perceived quality of life improved over time. Given the importance of quality of life in cancer settings and the negative influence of psychiatric comorbidity on it, the effect of psychopharmacologic treatment on this parameter should be considered a significant aim of research and clinical activity.

No effect was shown on physical symptoms, such as pain, nausea, constipation, appetite loss, and diarrhea. On the one hand, our results are in agreement with data reported by Holland et al.,[14] who found that a noradrenergic TCA (i.e., desipramine) was less effective than an SSRI (i.e., fluoxetine) in improving pain among cancer patients. However, nausea and vomiting were reported, as treatment-emergent signs and symptoms, by 38.1% and 28.6%, respectively, of patients receiving fluoxetine. In our study, the lack of gastrointestinal side effects (e.g., nausea, constipation,appetite loss, and diarrhea) can represent an advantage in treating cancer patients undergoing chemotherapy. With regard to the social dimensions, the reported effect of reboxetine in improving social adaptation in non–physically ill, depressed patients[46,47] was not confirmed here by using the EORTC-QLQ-C30 role and social subscales. However, because of the different instruments used in other studies, this issue deserves to be explored in a more specific way in oncology.

With regard to safety and tolerability, reboxetine was discontinued in only 2 patients. The first was a patient with a family history of mental disorder (a sister with schizophrenia) who developed a hypomanic switch. The possible risk of inducing hypomania by using reboxetine has been reported,[48] while other recent studies have pointed out the development of psychotic symptoms (delusions and hallucinations) in a patient with Parkinson's disease[26] and mania switch in a patient with HIV infection.[27] Further studies are necessary to understand the mechanisms underlying this possible adverse event in cancer patients. Intolerable side effects (increasing anxiety, insomnia, and tachycardia) were also reported by a second patient in our study who had been previously treated with other antidepressants, which were thus discontinued. One third of the patients showed transient side effects, including mild anxiety and insomnia, tension, and sweating.

Limitations of the study include the small number of patients and the use of an open-label design. Without a control group, it is difficult to exclude that natural

changes in quality of life, coping, and depression may occur in cancer patients. Furthermore, the good performance status of the patients in this study limits generalizability of the efficacy and tolerability of reboxetine among depressed cancer patients in an advanced stage of illness (e.g., palliative care cancer patients). Larger double-blind, placebo-controlled studies are necessary to confirm the results presented here. More specific evaluations of possible interactions with chemotherapy and other pharmacologic agents used in cancer patients should also be taken into account by further studies, as suggested by a number of authors in the last few years.[49–51]

In spite of these limitations, this study provides promising initial findings suggesting the efficacy and safety of reboxetine in depressed cancer patients. Its use in those who did not respond to other treatment or for whom other antidepressants may be contraindicated due to their negative side effects is a further valuable option for cancer patients.

Drug names: amitriptyline (Elavil and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), mirtazapine (Remeron and others), paroxetine (Paxil and others).

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