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Duloxetine for the treatment of mood disorder in cancer patients: a 12-week case-control clinical trial

Riccardo Torta*, Paolo Leombruni, Roberto Borio and Lorys Castelli

Clinical and Oncological Psychology Unit, Department of Neuroscience, University of Turin, Turin, Italy

Objective The aim of this study was to investigate the efficacy and tolerability of duloxetine in cancer patients with mood disorder (MD) by means of a comparison with a matched control group of patients with MD.

Methods Fifty-nine consecutive patients with MD were enrolled in this prospective case-control study and received duloxetine 60/120 mg per day for 12 weeks. Twenty-seven patients were affected by cancer, whereas 32 had an MD without cancer. All the patients were assessed by means of efficacy and effectiveness tolerability scales for depression (Montgomery–Asberg Depression Rating Scale and Hospital Anxiety and Depression Scale), anxiety (State-Trait Anxiety Inventory-Y1/Y2) and severity of symptoms (Clinical Global Impression (CGI)-Severity) at baseline (T0), after 4 weeks (T1) and 12 weeks (T2). The CGI-Improvement, CGI-Effectiveness Index and Dosage Record Treatment Emergent Symptom Scale were administered at T1 and T2.

Results A significant global improvement in all the efficacy measures was found. The results showed no significant interaction 'Time X Group', suggesting a similar improvement in efficacy scores for cancer-depressed patients and depressed patients without cancer. No difference was found between the two groups with regard to drop-out percentage, effectiveness and tolerability.

Conclusion Although the results of this case-control study are preliminary, they suggest that duloxetine can be considered a good option for the treatment of MD in cancer patients. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS—MD; cancer; duloxetine

INTRODUCTION

Studies have reported up to 58% of cancer patients as having depressive symptoms and up to 38% as having a major depressive disorder (MDD) (Massie, 2004). Also, recent data have confirmed a high prevalence (73.5%) of depressive symptoms in newly diagnosed cancer patients (Castelli et al., 2009).

Depression may be particularly difficult to detect in patients suffering from cancer, and it is difficult to distinguish from 'appropriate sadness' related to cancer diagnosis or to decide when a pharmacological treatment should be started. In addition, there are difficulties in deciding which somatic symptoms may be attributable to cancer and its consequences and which may be primarily due to depression (Lloyd-Williams, 2001). Detecting and treating depressive illness in cancer patients is a must, not only to improve the quality of life and reduce health service costs but also because depression is a systemic disease (Torta, 2006) producing impairment of immune response (Reiche et al., 2004) and a poorer survival rate (Faller and Bülzebruck, 2002; Spiegel and Giese-Davis, 2003).

The antidepressant duloxetine (DLX) is a dual serotonin and norepinephrine reuptake inhibitor, with relatively balanced affinity for binding to norepinephrine and serotonin transport sites (Bymaster et al., 2001; Bymaster et al., 2005) and without significant affinity for muscarinic, histaminergic, α-adrenergic and dopaminergic receptors (Wong and Bymaster, 2002). The efficacy and safety of DLX in the acute and long-term treatment of MDD have been established in a series of double-blind, placebo-controlled studies (Nemeroff et al., 2002; Hudson et al., 2007; Perahia et al., 2009).

Duloxetine has been shown to be effective in patients across a broad range of depressive symptoms and depression severity, although its side effects seem to be largest among severe depressed patients (Shelton et al., 2007).

In the choice of an antidepressant, it is also very important to evaluate its safety and tolerability, above all in patients in which mood depression is in comorbidity with a somatic disease, such as cancer. Some side effects, such as nausea, dry mouth or
constipation, can be considered minor in depressed patients, but they can have dangerous consequences in cancer-depressed patients. In addition, the cancer itself can have symptoms, such as drowsiness, nausea, vomiting, loss of appetite or fatigue, that can be potentiated by an antidepressant drug’s side effects.

Overall, DLX has shown a sufficient safety profile, as demonstrated in older patients, particularly for cardiovascular tolerability (Raskin et al., 2008; Mukai and Tampi, 2009; Mancini et al., 2009) and cognitive performance. Both these aspects are very important in cancer patients because of the cardiac and neurological side effects, which are secondary to several chemotherapeutic treatments (Soussain et al., 2009; Monsuez et al., 2010).

Duloxetine has also demonstrated an important indication in patients with mood disorder (MD) associated with painful physical symptoms (Fava et al., 2004; Brecht et al., 2007; Russell et al., 2008), so this drug could be particularly useful in cancer patients in which pain is frequently associated with depression (Goldstein et al., 2004; Wise et al., 2007; Beesdo et al., 2009). As a matter of fact, DLX has been found to be effective in other pathologies in which pain is frequently associated with depression, such as diabetic peripheral neuropathy (Raskin et al., 2005) and fibromyalgia (Üçeyler et al., 2008). Although depression is common in cancer patients, it often remains undetected and untreated, partly because of the misunderstanding that it is a ‘normal emotional reaction’ to a threatening disease (Thomas et al., 2010).

On this basis, the aim of the present study was to investigate the efficacy and tolerability of DLX in a population of cancer patients with MD by means of a comparison with a matched control group of patients with MD without medical illness.

To our knowledge, this is the first study considering the use of DLX in patients with cancer associated with MD.

MATERIALS AND METHODS

Subjects

The study was carried out at the Psychoncology Unit of St. Giovanni Battista Hospital of the University of Turin and approved by the ethics committee of the hospital. Each patient gave written informed consent.

Fifty-nine consecutive depressed patients showing MD were enrolled in the study. MD was defined by the presence of an MDD or adjustment disorder with depressed mood, according to the DSM-IV-TR criteria (APA, 2000). Twenty-seven patients were affected by cancer (C-MD group), whereas 32 had an MD without medical disease (MD group). Demographic and clinical characteristics of the two groups are shown in Table 1.

Cancer-depressed patients presented the following disease sites: 7 breast, 5 colorectal, 4 hematologic, 3 gastric, 3 lung, 2 ovarian, 2 prostate and 1 hepatopancreas. Twenty patients (74%) had received chemotherapy and 11 (41%) radiotherapy; 21 (78%) had undergone surgical intervention. Four of seven patients with breast cancer were taking estrogenic agents (tamoxifen or aromatase inhibitors) during the study. Even if there is no univocal agreement about the relation between the use of these drugs and the appearance of depressive symptoms, dual antidepressant have been shown to be effective and safe for the treatment of depression in estrogenic drugs users (Desmarais and Looper, 2010).

Inclusion criteria were the following: the presence of MD (adjustment disorder with depressed mood or MDD) following the diagnostic criteria of the DSM-IV-TR (APA, 2000); age between 18 and 85 years; and a Montgomery–Asberg Depression Rating Scale (MADRS) score of ≥11 (Zimmerman et al., 2004). It has to be noted that the diagnosis of MD and the administration of the MADRS were made by a psychiatrist with a large expertise in oncology settings to avoid the confounding factor of somatic symptoms. Indeed, in such patients, the role of somatic symptoms (loss of appetite, weight or energy, fatigue, sleep disturbances) is much less clear because it is possibly secondary to the cancer pathology itself rather than because of an MD. For this reason, somatic symptoms secondary to the cancer pathology could artificially influence the diagnosis of MD as well as increase the MADRS score.

Exclusion criteria were as follows: a prior history of psychotic disorder; a comorbid Axis I disorder other than depression; taking psychotropic drugs at the time of inclusion in the study or in the previous 2 months; any ongoing chemotherapeutic or radiotherapeutic treatment or during the last month; central nervous system tumours and endocrinological diseases (C-MD group); pregnancy and lactation; and hypertension or other cardiovascular diseases.

Design

This was a prospective, 12-week, case-control study that aimed to investigate the efficacy (primary outcome) and the tolerability of DLX in the treatment of depression in cancer patients by means of a comparison with a population of depressed patients without cancer.

First of all, the patients underwent a psychiatric interview to diagnose the presence of MD (MDD or
(DOTES) were administered at T1 and T2. Dosage Record Treatment Emergent Symptom Scale repeated after 4 weeks (T1) and 12 weeks (T2). Further, starting titration to reduce the fast dose—

Subjects who wished to withdraw from the study were in all patients by the beginning of the third week. 2 weeks of treatment and were progressively withdrawn for sleep disorder, if necessary, only during the

Benzodiazepines (lorazepam 1 mg/day) were allowed poor response, the dose was increased to 120 mg. Increased to 60 mg daily. After 1 month (T1), in case of

quality of life by means of the Impression

Clinical variables

Table 1. Demographic and clinical characteristics of the C-MD and the MD group at baseline assessment (T0). Mean (standard deviation) and t-test/chi-square analysis are shown

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>C-MD group</th>
<th>MD Group</th>
<th>T (d.f.)/chi square</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>27</td>
<td>32</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>16/11</td>
<td>18/14</td>
<td>0.05*</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.6 (10.9)</td>
<td>54.3 (15.3)</td>
<td>–2.63 (57)</td>
<td>0.01</td>
</tr>
<tr>
<td>Marital Status (no. of patients)</td>
<td>–</td>
<td>–</td>
<td>1.27*</td>
<td>NS</td>
</tr>
<tr>
<td>Married</td>
<td>21</td>
<td>24</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Divorced</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Unmarried</td>
<td>2</td>
<td>5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Widower</td>
<td>3</td>
<td>2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Occupation (no. of patients)</td>
<td>–</td>
<td>–</td>
<td>7.32*</td>
<td>NS</td>
</tr>
<tr>
<td>Public worker</td>
<td>6</td>
<td>8</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Private worker</td>
<td>1</td>
<td>6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Unemployed</td>
<td>0</td>
<td>3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Housewife</td>
<td>5</td>
<td>3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pensioner</td>
<td>15</td>
<td>12</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Clinical variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MADRS</td>
<td>32.0 (8.9)</td>
<td>33.2 (6.5)</td>
<td>0.64 (57)</td>
<td>NS</td>
</tr>
<tr>
<td>HADS-D</td>
<td>13.9 (4.4)</td>
<td>15.9 (2.9)</td>
<td>1.97 (57)</td>
<td>NS</td>
</tr>
<tr>
<td>HADS-A</td>
<td>12.6 (4.7)</td>
<td>14.6 (3.4)</td>
<td>1.84 (57)</td>
<td>NS</td>
</tr>
<tr>
<td>STAI-Y1</td>
<td>63.1 (9.6)</td>
<td>63.9 (8.7)</td>
<td>0.33 (57)</td>
<td>NS</td>
</tr>
<tr>
<td>STAI-Y2</td>
<td>52.8 (11.5)</td>
<td>50.6 (12.5)</td>
<td>–0.69 (57)</td>
<td>NS</td>
</tr>
<tr>
<td>CGI-S</td>
<td>4.6 (1.0)</td>
<td>4.7 (0.7)</td>
<td>0.61 (57)</td>
<td>NS</td>
</tr>
</tbody>
</table>

MADRS, Montgomery—Asberg Depression Rating Scale; HADS-D, Hospital Anxiety and Depression Scale-depression subscale; HADS-A, Hospital Anxiety Depression Scale-anxiety subscale; STAI-Y1/Y2, State-Trait Anxiety Inventory-Y1/Y2; CGI-S, Clinical Global Impression-Severity; NS, not significant.

adjustment disorder with depressed mood). On the same day, the patients were administered the following rating scales by an expert clinician (R. B.) blind to the aim of the study: the MADRS, the Hospital Anxiety and Depression Scale (HADS), the State—Trait Anxiety Inventory (STAI-Y1/Y2) and the Clinical Global Impression-Severon (CGI-S). This assessment was repeated after 4 weeks (T1) and 12 weeks (T2). Further, the CGI-Improvement, CGI-Effectiveness Index and Dosage Record Treatment Emergent Symptom Scale (DOTES) were administered at T1 and T2.

Finally, cancer-depressed patients were assessed for quality of life by means of the ‘European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30’ (EORTC QLQ-C30) at T0 and at the end of the study (T2).

After the T0 assessment, the patients received DLX for 1 week, with an initial dosage of 30 mg in a single, fixed morning dose, according to the need for a slow-starting titration to reduce the fast dose-related occurrence of side effects. The dosage was then increased to 60 mg daily. After 1 month (T1), in case of poor response, the dose was increased to 120 mg. Benzodiazepines (lorazepam 1 mg/day) were allowed for sleep disorder, if necessary, only during the first 2 weeks of treatment and were progressively withdrawn in all patients by the beginning of the third week. Subjects who wished to withdraw from the study were allowed to do so at any time.

Assessment

Efficacy measures.

• The MADRS: a semi-structured clinician-rated interview composed of 10 questions rated from 0 to 6 (Montgomery and Asberg, 1979). The total score ranges from 0 (absence of depression) to 60 (severe depression). Following the recommendations provided by Zimmerman, a MADRS cut-off of 11 was used to tally a patient as depressed (≥11) or not (<11) (Zimmerman et al., 2004). The MADRS was administered by a clinician blind to the aim of the study.

• The HADS: a 14-item (rated 0—3) self-report scale widely used in clinical practise to screen the presence of depressive and anxiety symptoms (Kearns et al., 1982; Zimmerman et al., 2004). It is composed of two subscales: a 7-item depression subscale (HADS-D) and a 7-item anxiety subscale (HADS-A). The total HADS-D and HADS-A score ranges from 0 (absence of depression/anxiety) to 21 (severe depression/anxiety).

• The STAI-Y1/Y2 was used to assess anxiety as a reaction to episodic stress conditions (STAI-Y1) and as a predisposition to persistent anxious behaviour (STAI-Y2). Each subscale (Y1 and Y2) is composed of 20 items rated from 0 to 4. The total score ranges from 0 (absence of anxiety) to 80 (severe anxiety) (Spielberger, 1989).
• The CGI-S and CGI-Global Improvement (CGI-GI): the first subscale, CGI-S, is a 7-point item that was used to obtain a global judgement about the severity of the depressive symptoms. The second subscale, CGI-GI, is a 7-point item administered to quantify the degree of improvement of depressive symptoms with respect to the baseline assessment (Guy, 1976a, 1976b).

• The EORTC QLQ-C30: a 30-item self-report questionnaire developed to assess the quality of life of cancer patients. It is subdivided into five functional subscales (role, physical, cognitive, emotional and social functioning). In addition, there are three multi-item symptoms scales (fatigue, pain and nausea and vomiting), individual questions concerning common symptoms in cancer patients and two questions assessing overall quality of life.

**Effectiveness and tolerability measures.**
• The CGI-Effectiveness Index evaluates the effectiveness of a specific pharmacological treatment, considering both the therapeutic effect and the side effects. It is rated from 1 to 4 for both the therapeutic effect and the side effects (Guy, 1976a, 1976b).

• The DOTES is used to check the presence and severity (rated 1–4/absent to severe) of specific side effects and their possible relationship to the pharmacological treatment (rated 1–5/no relation to strong relation) and any measure to manage these adverse effects (Guy, 1976a, 1976b).

**STATISTICAL ANALYSIS**
All statistical analyses were carried out using the SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Firstly, t-tests for independent sample and chi-square analysis were run to compare demographic and clinical variables of the two groups at T0. The same analysis was made to compare patients who completed the study with those who did not. The General Linear Model analyses for repeated measures were run to evaluate the effect of time (T0-T1-T2) on the different variables and the interaction between time and groups (C-MD/MD). Bonferroni post hoc analyses were used to compare T0, T1 and T2 scores of primary and secondary outcome measures (two by two comparisons). Values of $p \leq 0.05$ were considered statistically significant.

**RESULTS**
**Baseline assessment**
The clinical and demographic characteristics of the two groups of patients (C-MD and MD) are listed in Table 1.

With regard to the demographic variables, the two groups were matched for sex, marital status and occupation. A statistically significant difference was found for age ($p = 0.01$), which was lower in the MD group. With regard to the efficacy variables, the patients were matched for MADRS, HADS-A and D, STAI-Y1 and Y2 and CGI-S at T0 assessment (Table 1).

**Lost to follow-up**
Twelve patients of 59 (20%) did not complete the study: 4 of 27 C-MD patients (15%) and 8 of 32 MD patients (25%). All non-completers dropped out before the T1 assessment. The different proportion of completers and non-completers between the two groups was not statistically significant (chi square $= 0.938; p = 0.33$). The reasons for non-completion were collected through telephone interviews made before the T1 assessment.

The four patients in the C-MD group dropped out because of agitation and tachycardia (one patient), insomnia and agitation (one), gastric disease and anxiety (one) and insomnia and tachycardia (one).

The eight patients in the MD group dropped out because of agitation, insomnia, gastric disease and hyperhidrosis (two patients), headache (one), urinary retention (one), agitation (one) and gastric disease (one). Finally, two patients did not complete the study because of a self-perception of drug inefficacy.

No significant differences were found with regard to the main demographic and clinical variables in the comparison between the patients who completed the study and those who did not. These data are detailed in Table 2.

As far as completers were concerned, the daily dosage of DLX was increased from 60 to 120 mg/day in nine patients of the C-MD group (40%) and in nine patients of the MD group (37.5%) at T1 assessment. One patient in each group increased the dosage from 60 to 120 mg/day between T1 and T2 assessment. So the mean DLX dosage was 83.5 mg/day and 82.5 mg/day in the C-MD and MD group, respectively.

**Efficacy outcome measures**
The General Linear Model for repeated measures evidenced a significant improvement in all the efficacy scores (MADRS, HADS-D and A, STAI-Y1 and CGI-S) except for STAI-Y2, which is more linked to temperamental than pathological aspects. The results also showed no significant interaction regarding Time X Group, suggesting a similar improvement in efficacy scores for cancer-depressed patients and depressed patients without cancer. These results are listed in Table 3.
This said, some differences between the two groups were found using Bonferroni post hoc analysis. For the C-MD group, all the efficacy measures showed a significant improvement both between T0 and T2 and T0 and T1 (Bonferroni post hoc analysis; Table 3). The same results were found for the MD group; nevertheless, in this latter group, the rate of improvement both at T1 and at T2 is higher, even if not numerically significant, than in the C-MD group (Bonferroni post hoc analysis; Table 3).

As far as the CGI-GI subscales are concerned, the results at T1 showed that 12 patients (52%) of the C-MD group and 10 patients (42%) of the MD group evidenced a moderate or high improvement (score of 1 or 2). A mild improvement (score of 3) was found in seven patients (30%) of the C-MD group and eight patients (33%) of the MD group. No change (score of 4) was observed in three patients (13%) of the C-MD group and six patients (25%) of the MD group. Finally, only one completing patient (4%) of the C-MD group reported a mild worsening (score of 5) of depressive symptoms. Chi square did not evidence significant differences in these proportions (chi square = 2.95; p = 0.56).

At T2, 16 patients (70%) of the C-MD group and 14 patients (58%) of the MD group evidenced a moderate or high improvement in the CGI-GI. Four patients of the C-MD (17%) group and five patients (21%) of the MD group showed a mild improvement (score of 3). No change was found in three patients in both the C-MD group (13%) and the MD group (12%). Two patients

Table 3. Duloxetine efficacy variables for C-MD (23 patients) and MD (24 patients) groups

<table>
<thead>
<tr>
<th>GLM repeated measures</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>Time</th>
<th>Time X Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>4 weeks</td>
<td>12 weeks</td>
<td>F; p</td>
<td>F; p</td>
</tr>
<tr>
<td>MADRS C-MD</td>
<td>32.3 (8.9)</td>
<td>20.8 (12.3)*</td>
<td>14.5 (10.8)*</td>
<td>50.7; &lt;0.001</td>
<td>0.3; NS</td>
</tr>
<tr>
<td>MD</td>
<td>34.5 (6.3)</td>
<td>21.6 (10.2)*</td>
<td>13.9 (8.9)*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MADRS C-MD</td>
<td>14.4 (3.8)</td>
<td>10.6 (5.1)*</td>
<td>7.2 (4.6)*</td>
<td>42.7; &lt;0.001</td>
<td>0.7; NS</td>
</tr>
<tr>
<td>MD</td>
<td>16.0 (2.8)</td>
<td>10.9 (3.6)*</td>
<td>7.7 (5.0)*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HADS C-MD</td>
<td>13.2 (4.5)</td>
<td>9.6 (4.4)*</td>
<td>6.6 (4.5)*</td>
<td>40.2; &lt;0.001</td>
<td>1.15; NS</td>
</tr>
<tr>
<td>MD</td>
<td>15.2 (3.4)</td>
<td>11.2 (3.9)*</td>
<td>6.3 (3.5)*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MADRS C-MD</td>
<td>63.3 (10.1)</td>
<td>55.0 (11.5)*</td>
<td>48.5 (12.6)*</td>
<td>28.5; &lt;0.001</td>
<td>1.2; NS</td>
</tr>
<tr>
<td>MD</td>
<td>63.4 (9.1)</td>
<td>49.4 (12.7)*</td>
<td>41.7 (11.4)*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>STAI-Y2 C-MD</td>
<td>52.4 (11.9)</td>
<td>49.6 (11.6)*</td>
<td>46.8 (11.2)*</td>
<td>1.7; NS</td>
<td>0.8; NS</td>
</tr>
<tr>
<td>MD</td>
<td>51.4 (13.7)</td>
<td>48.6 (12.3)*</td>
<td>47.4 (9.7)*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CGI-S C-MD</td>
<td>4.6 (1.0)</td>
<td>3.2 (1.4)*</td>
<td>2.4 (1.6)*</td>
<td>38.2; &lt;0.001</td>
<td>0.08; NS</td>
</tr>
<tr>
<td>MD</td>
<td>4.7 (0.7)</td>
<td>3.2 (1.4)*</td>
<td>2.4 (1.3)*</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

GLM, General Linear Model; MADRS, Montgomery–Asberg Depression Rating Scale; HADS-D, Hospital Anxiety and Depression Scale-depression subscale; HADS-A, Hospital Anxiety and Depression Scale-anxiety subscale; STAI-Y1/Y2, State-Trait Anxiety Inventory-Y1/Y2; CGI-S, Clinical Global Impression-Severity; NS, not significant.

T1 versus T2: all variables showed a significant reduction in the MD group, whereas no significant differences were found in the C-MD group.

*p < 0.05, T1 versus T0 scores and T2 versus T0 scores (Bonferroni post hoc).
(8%) of the MD group showed a mild worsening. In this case, too, no significant difference was found between the two groups (chi square = 3.41; p = 0.63).

Finally, the EORTC QLQ-C30 results pointed out an overall significant improvement in quality of life for cancer-depressed patients (total score, T0 versus T2: p = 0.001). As far as the single subscales are concerned, significant improvements were found in the following domains: physical, role, emotional and cognitive functioning, fatigue, nausea and vomiting, pain, appetite loss, global health and quality of life. These results are detailed in Table 4.

**Effectiveness and tolerability outcome measures**

The patients’ subdivisions according to the CGI-T5 Effectiveness Index are detailed in Table 5. No statistically significant differences between the two groups as for the proportion of patients in the different categories were found at T1 (chi square = 3.4; p = 0.6) or at T2 (chi square = 11.8; p = 0.4).

Specific side effects were detected by means of the DOTES. Here, we summarise the number and percentage of patients who showed a side effect of moderate or severe entity (score of 3 or 4) with a probable or strong (score of 4 or 5) relation to the DLX therapy. As far as T1 assessment is concerned, one patient (4%) either in the C-MD group or in the MD group evidenced agitation, one patient (4%) of the C-MD group showed insomnia, and one patient of the MD group showed tachycardia. Moderate hypertension was found in one patient (4%) of the MD group. The most of these symptoms disappeared at T2 assessment without any pharmacological intervention, except agitation in one patient (4%) of the MD group and tachycardia in one patient (4%) of the same group.

No patients evidenced severe modifications of blood pressure at either T1 or T2. Finally, as previously detailed in the section ‘lost to follow-up’, four patients (15%) in the C-MD group and six patients (19%) in the MD group withdrew from the study because of a side effect.

**DISCUSSION**

There is limited trial data on the efficacy of prescribed antidepressants in reducing the incidence of MDD and depressive symptoms in cancer patients. A systematic review of the efficacy of antidepressant interventions for cancer patients with depression/depressive symptoms was first carried out by Williams and Dale in 2006: of 29 clinical trial studies on antidepressant efficacy in cancer patients only six randomised placebo-controlled trials were considered eligible for this meta-analysis. Four studies were carried out in the USA (paroxetine: Musselman et al., 2001; fluoxetine: Fisch et al., 2003; paroxetine: Morrow et al., 2003; paroxetine: Roscoe et al., 2005) and two in Belgium (fluoxetine: Razavi et al., 1996; mianserine: van Heeringen and Zivkov, 1996).

Paroxetine was found to be effective in reducing MDD in patients with malignant melanoma who were receiving high-dose interferon alpha therapy.

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**Table 4. Quality of life in the cancer-depressed patients. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 subscales scores of the 23 C-MD patients. Mean (standard deviation) and t-test comparisons (T0 versus T2) are listed.**

<table>
<thead>
<tr>
<th>Quality of life</th>
<th>T0 Baseline</th>
<th>T2 End point</th>
<th>t (d.f.:22); p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>53.3 (15.9)</td>
<td>41.3 (17.1)</td>
<td>2.5; 0.021*</td>
</tr>
<tr>
<td>Role functioning</td>
<td>51.0 (18.9)</td>
<td>37.0 (14.8)</td>
<td>3.1; 0.005*</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>66.8 (16.8)</td>
<td>51.3 (19.3)</td>
<td>2.6; 0.015*</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>57.9 (19.4)</td>
<td>39.1 (15.7)</td>
<td>3.7; 0.001*</td>
</tr>
<tr>
<td>Social functioning</td>
<td>66.8 (24.6)</td>
<td>54.3 (21.8)</td>
<td>1.8; NS</td>
</tr>
<tr>
<td>Fatigue</td>
<td>72.8 (18.3)</td>
<td>58.3 (16.4)</td>
<td>2.6; 0.016*</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>42.2 (18.3)</td>
<td>31.5 (11.2)</td>
<td>2.3; 0.032*</td>
</tr>
<tr>
<td>Pain</td>
<td>59.2 (25.9)</td>
<td>42.9 (20.6)</td>
<td>2.2; 0.035*</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>46.7 (20.4)</td>
<td>36.9 (18.3)</td>
<td>1.7; NS</td>
</tr>
<tr>
<td>Insomnia</td>
<td>65.2 (26.9)</td>
<td>47.8 (23.7)</td>
<td>2.0; NS</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>57.6 (24.3)</td>
<td>41.3 (19.4)</td>
<td>2.5; 0.022*</td>
</tr>
<tr>
<td>Constipation</td>
<td>42.4 (27.6)</td>
<td>29.3 (12.3)</td>
<td>2.0; NS</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>27.2 (10.4)</td>
<td>27.2 (10.2)</td>
<td>0.0; NS</td>
</tr>
<tr>
<td>Financial difficulties</td>
<td>30.4 (13.0)</td>
<td>27.2 (10.4)</td>
<td>0.9; NS</td>
</tr>
<tr>
<td>Quality of life</td>
<td>53.0 (20.0)</td>
<td>67.1 (17.0)</td>
<td>−2.8; 0.011*</td>
</tr>
<tr>
<td>Global health</td>
<td>51.1 (18.3)</td>
<td>67.7 (18.4)</td>
<td>−2.3; 0.029*</td>
</tr>
<tr>
<td>Total score</td>
<td>863.1 (80.6)</td>
<td>666.6 (117.7)</td>
<td>5.5; 0.001*</td>
</tr>
</tbody>
</table>

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

*statistically significant differences.
(Musselman et al., 2001) and in reducing caseness for depression in breast cancer patients receiving chemotherapy (Roscoe et al., 2005). Fluoxetine was not effective in reducing caseness for depression in a trial that included patients with breast, gynaecological or haematological cancer (Razavi et al., 1996). However, the study by Razavi and colleagues (1996) showed some limitations: it was a short-term trial (5 weeks) and low doses of fluoxetine were used. Paroxetine and fluoxetine were both effective in reducing depressive symptoms in three trials that included patients with mixed cancers (breast, lung, haematological, gynaecological and gastrointestinal) (Fisch et al., 2003; Morrow et al., 2003; Roscoe et al., 2005). The tetracyclic antidepressant mianserin was also shown to be effective in reducing depressive symptoms in breast cancer (van Heeringen and Zivkov, 1996). Although tolerability data were only reported in four of the six pharmacological studies, overall the tolerability of antidepressants in patients with cancer appears to be sufficiently good (Pezzella et al., 2001; Pae et al., 2004; Torta et al., 2008).

To our knowledge, the present study is the first trial using DLX in cancer patients. The aim of this study was to investigate the efficacy and tolerability of DLX in the treatment of depression in cancer patients by means of a comparison with a control group of depressed patients.

The results of this study suggest that DLX is effective and well tolerated in patients with MD and cancer pathologies as well as in patients with MD. Both the HADS and MADRS showed a significant improvement of depressive symptoms in this 12-week trial. In contrast to the concept that patients with a severe somatic disease are not full responders to an antidepressant treatment, we observed that both the self-evaluation for depression (HADS-D) and the hetero-evaluation (MADRS) demonstrated a significant improvement in both groups.

On the other hand, the clinician-rated CGI-S assessing the severity of depressive symptoms showed the same significant improvement in both groups. Interestingly, the CGI for the evaluation of the global improvement (CGI-GI) demonstrated a trend towards a higher improvement in the cancer-depressed group than in the depressed group without cancer. Specifically 53% versus 29% of patients at T1 and 69% versus 50% of patients at T2 evidenced a high or moderate therapeutic response, for the cancer-depressed and depressed groups, respectively.

In addition, DLX was found to be effective in reducing anxiety: the STAI-Y1, a self-evaluation scale for state anxiety, demonstrated a significant reduction in both groups. This is an interesting result because cancer patients often have anxiety symptoms, mostly stress related, but the use of gabaergic benzodiazepines can increase the sense of fatigue that is still very troublesome in such patients. Actually, in this trial, lorazepam was allowed if necessary, only in the two first weeks of treatment; afterwards, it was withdrawn in all patients, without producing an anxiety increase.

The anxiolytic effect of duloxetine acts through the normalisation of noradrenergic and serotonergic pathways (Carter and McCormack, 2009; Mancini et al., 2010) and through an increase of anxiolytic neurosteroids in the CNS, such as allopregnanolone (as demonstrated for selective serotonin reuptake inhibitor drugs) (Romeo et al., 1998; Uzunova et al., 2006; Girdler and Klatzkin, 2007), without causing fatigue, as confirmed in our study by the significant reduction of self-perceived fatigue (EORTC QLQ-C30: fatigue score).

Another very important aspect concerning MD in cancer patients is the relationship between mood and...
pain. In this study, the results on the EORTC scale evidenced a significant reduction of self-perceived pain (EORTC QLQ-C30: pain score), confirming the antalgic activity of duloxetine, both direct (through intrinsic analgesic activity) and indirect (through mood improvement) (Perahia et al., 2006; Lunn et al., 2009).

As the number of drop-out patients suggests, (15% in the cancer-depressed group and 19% in the depressed group without cancer), our results show that cancer-depressed patients tolerate duloxetine as well as depressed patients. Further, to achieve this result for cancer-depressed patients, a higher DLX dosage with respect to depressed patients does not seem necessary: actually, the mean dosage of DLX was pretty much the same between the two groups (83.5 mg/day for the cancer-depressed group and 82.5 mg/day for the depressed group).

All non-completers dropped out within the first 4 weeks of treatment. In accordance with the literature, this finding demonstrated once again that adherence to the antidepressant therapy is lower in the first weeks of treatment, with the appearance of side effects before an improvement in depression (Masand, 2003; Ollison et al., 2006).

It should also be noted that, beyond the improvement in mood, our results suggest that DLX produced a significant improvement in many aspects related to quality of life (EORTC). Cancer patients with MD showed a significant improvement in physical, role, emotional and also in cognitive functioning, comparing the baseline with the 12-week assessment.

Overall, the balance between DLX efficacy and tolerability (Table 5) highlighted no correlation between therapeutic benefits and severity of side effects. Indeed DLX allowed the patients to decrease depressive symptoms without experiencing relevant side effects. On that basis, DLX can be considered an effective drug for the treatment of depression also in cancer patients.

This pilot study presents two main limitations: (i) the small number of patients and the heterogeneity of the sample, either for cancer diagnosis or for psychiatric/depression diagnosis (MDD or adjustment disorder with depressed mood) and (ii) the open-trial design, that is, the lack of a placebo arm. Nevertheless, it should be noted that the use of Placebos in a cancer-depressed population is ethically controversial because depression not only interferes with quality of life but, as a stress-related psychosocial factor, also adversely affects cancer incidence and survival, worsening the immunity defences in these patients (Chida et al., 2008).

Another limitation is the lack of a specific scale assessing pain. Even if the relationship between MD and pain was not a specific goal of this study (Torta and Munari, 2010), considerations about a DLX-induced pain reduction are based on a single EORTC item and should be interpreted with caution. Furthermore, the probable impact of DLX on pain can represent a confounder, especially for cancer-depressed patients, because DLX may have lowered the patients’ distress level without having an independent impact on depressive symptoms.

In conclusion, our preliminary results highlighted that DLX can be a useful and safe drug for depression also in cancer-depressed patients. Specifically, our data suggest that DLX has comparable tolerability in patients who are affected by cancer and those who are physically healthy. In addition, the presence of cancer does not seem to interfere with the efficacy of DLX.

Wider and controlled studies are needed to confirm these preliminary results about the efficacy and tolerability of DLX in cancer patients.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

REFERENCES


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<td>Q6</td>
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</table>

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Add in the footnote: "* data were compared using chi-square."

page 4, line 9 and 10: delete ", 1976b"
page 4, line 26: delete ", 1976b"
page 4, line 32: delete " 1976a,"

Table 2. The asterisk means that we perform chi-square instead of t-test for that specific variable (see first line of the table). No one of the variables reached the significance level, and so we do not need to add p value. Please delete the asterisk after "chi square" only in the caption of the table.
Add in the footnote: "* data were compared using chi-square."
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