Slow versus standard up-titration of paroxetine for the treatment of depression in cancer patients: a pilot study

Dear Author

Here are the proofs of your article.

- You can submit your corrections **online,** via **e-mail** or by **fax**.
- For **online** submission please insert your corrections in the online correction form. Always indicate the line number to which the correction refers.
- You can also insert your corrections in the proof PDF and **email** the annotated PDF.
- For **fax** submission, please ensure that your corrections are clearly legible. Use a fine black pen and write the correction in the margin, not too close to the edge of the page.
- Remember to note the **journal title**, **article number**, and **your name** when sending your response via e-mail or fax.
- **Check** the metadata sheet to make sure that the header information, especially author names and the corresponding affiliations are correctly shown.
- **Check** the questions that may have arisen during copy editing and insert your answers/corrections.
- **Check** that the text is complete and that all figures, tables and their legends are included. Also check the accuracy of special characters, equations, and electronic supplementary material if applicable. If necessary refer to the *Edited manuscript*.
- The publication of inaccurate data such as dosages and units can have serious consequences. Please take particular care that all such details are correct.
- Please **do not** make changes that involve only matters of style. We have generally introduced forms that follow the journal's style.
- Substantial changes in content, e.g., new results, corrected values, title and authorship are not allowed without the approval of the responsible editor. In such a case, please contact the Editorial Office and return his/her consent together with the proof.
- If we do not receive your corrections **within 48 hours**, we will send you a reminder.
- Your article will be published **Online First** approximately one week after receipt of your corrected proofs. This is the **official first publication** citable with the DOI. **Further changes are, therefore, not possible.**
- The **printed version** will follow in a forthcoming issue.

Please note

After online publication, subscribers (personal/institutional) to this journal will have access to the complete article via the DOI using the URL:

`http://dx.doi.org/10.1007/s00520-011-1118-8`

If you would like to know when your article has been published online, take advantage of our free alert service. For registration and further information, go to: http://www.springerlink.com.

Due to the electronic nature of the procedure, the manuscript and the original figures will only be returned to you on special request. When you return your corrections, please inform us, if you would like to have these documents returned.

Metadata of the article that will be visualized in OnlineFirst

1	Article Title	**Slow versus standard up-titration of paroxetine for the treatment of depression in cancer patients: a pilot study**	
2	Article Sub- Title		
3	Article Copyright - Year	**Springer-Verlag 2011 (This will be the copyright line in the final PDF)**	
4	Journal Name	Supportive Care in Cancer	
5	Corresponding Author	Family Name	**Castelli**
6		Particle	
7		Given Name	**Lorys**
8		Suffix	
9		Organization	University of Turin
10		Division	Psycho-oncology Unit, Department of Neuroscience and Oncology
11		Address	Corso Bramante 88, Turin 10126, Italy
12		Organization	University of Turin
13		Division	Clinical and Oncological Psychology, Department of Neuroscience
14		Address	Turin , Italy
15		e-mail	castelli_lorys@hotmail.com
16	Author	Family Name	**Amodeo**
17		Particle	
18		Given Name	**Laura**
19		Suffix	
20		Organization	University of Turin
21		Division	Clinical and Oncological Psychology, Department of Neuroscience
22		Address	Turin , Italy
23		e-mail	
24	Author	Family Name	**Leombruni**
25		Particle	
26		Given Name	**Paolo**
27		Suffix	
28		Organization	University of Turin
29		Division	Clinical and Oncological Psychology, Department of Neuroscience
30		Address	Turin , Italy
31		e-mail	
32		Family Name	

			Cipriani
33		Particle	
34		Given Name	**Daniela**
35		Suffix	
36	Author	Organization	University of Turin
37		Division	Clinical and Oncological Psychology, Department of Neuroscience
38		Address	Turin , Italy
39		e-mail	
40		Family Name	**Biancofiore**
41		Particle	
42		Given Name	**Alessia**
43		Suffix	
44	Author	Organization	University of Turin
45		Division	Clinical and Oncological Psychology, Department of Neuroscience
46		Address	Turin , Italy
47		e-mail	
48		Family Name	**Torta**
49		Particle	
50		Given Name	**Riccardo**
51		Suffix	
52	Author	Organization	University of Turin
53		Division	Clinical and Oncological Psychology, Department of Neuroscience
54		Address	Turin , Italy
55		e-mail	
56		Received	22 June 2010
57	Schedule	Revised	
58		Accepted	13 February 2011

59 Abstract

Objectives: This study aimed to compare the tolerability and efficacy of two different titrations of paroxetine (slow and standard) in a population of cancer patients with depression.
Methods: This randomized open trial included 30 cancer patients with depression (major depressive disorder, dysthymic disorder, or adjustment disorder with depressed mood) and aimed to compare the safety of slow up-titration (arm A) versus standard up-titration (arm B) of paroxetine chlorhydrate. In both arms, the maximum final dose was 20 mg/day. Patients were evaluated at baseline and after 2, 4, and 8 weeks with rating scales for depression and anxiety (MADRS, HADS, HAM-A, CGI), quality of life (EORTC-QLQ-30), and side effects (DOTES, SIDE).
Results: Thirty consecutive cancer patients (F = 21; M = 9) meeting DSM-IV TR criteria for mood disorders (MD) were enrolled in the study and randomly assigned to slow or standard paroxetine titration. Both treatment groups showed a significant mood improvement (change in MADRS total score) from baseline to end point (arm A—$F(2,18) = 33.68$ $p < 0.001$; arm B—$F(2,12) = 6.97$ $p < 0.005$). A significantly higher rate of patients in arm A compared with arm B showed no side effects after 2 weeks (40% vs. 6.7%, respectively). A

		multinomial logistic regression confirmed such differences between arms (chi square = 20.89 *p* = 0.004). The self-evaluating scale (SIDE) confirmed this difference: 60% of subjects in arm B perceived side effects compared to only 11.1% of patients in arm A. **Conclusions:** The results of this study suggest that slow paroxetine up-titration is better tolerated and at least as effective as the standard paroxetine up-titration in cancer patients with depression.
60	Keywords separated by ' - '	Paroxetine - Cancer - Mood disorder - Slow titration
61	Foot note information	

Support Care Cancer
DOI 10.1007/s00520-011-1118-8

ORIGINAL ARTICLE

Slow versus standard up-titration of paroxetine for the treatment of depression in cancer patients: a pilot study

Laura Amodeo · Lorys Castelli · Paolo Leombruni · Daniela Cipriani · Alessia Biancofiore · Riccardo Torta

Received: 22 June 2010 / Accepted: 13 February 2011

Abstract
Objectives This study aimed to compare the tolerability and efficacy of two different titrations of paroxetine (slow and standard) in a population of cancer patients with depression.
Methods This randomized open trial included 30 cancer patients with depression (major depressive disorder, dysthymic disorder, or adjustment disorder with depressed mood) and aimed to compare the safety of slow up-titration (arm A) versus standard up-titration (arm B) of paroxetine chlorhydrate. In both arms, the maximum final dose was 20 mg/day. Patients were evaluated at baseline and after 2, 4, and 8 weeks with rating scales for depression and anxiety (MADRS, HADS, HAM-A, CGI), quality of life (EORTC-QLQ-30), and side effects (DOTES, SIDE).
Results Thirty consecutive cancer patients (F=21; M=9) meeting DSM-IV TR criteria for mood disorders (MD) were enrolled in the study and randomly assigned to slow or standard paroxetine titration. Both treatment groups showed a significant mood improvement (change in MADRS total score) from baseline to end point (arm A—$F(2,18)=33.68$ $p<0.001$; arm B—$F(2,12)=6.97$ $p<0.005$). A significantly higher rate of patients in arm A compared with arm B showed no side effects after 2 weeks (40% vs. 6.7%, respectively). A multinomial logistic regression confirmed such differences between arms (chi square=20.89 $p=0.004$). The self-evaluating scale (SIDE) confirmed this difference: 60% of subjects in arm B perceived side effects compared to only 11.1% of patients in arm A.
Conclusions The results of this study suggest that slow paroxetine up-titration is better tolerated and at least as effective as the standard paroxetine up-titration in cancer patients with depression.

Keywords Paroxetine · Cancer · Mood disorder · Slow titration

L. Amodeo · L. Castelli · P. Leombruni · D. Cipriani · A. Biancofiore · R. Torta
Clinical and Oncological Psychology,
Department of Neuroscience, University of Turin,
Turin, Italy

L. Castelli (✉)
Psycho-oncology Unit,
Department of Neuroscience and Oncology, University of Turin,
Corso Bramante 88,
10126 Turin, Italy
e-mail: castelli_lorys@hotmail.com

Introduction

Several epidemiological and clinical data suggest a strong bidirectional relationship between cancer and mood disorders (MD) [1, 2]. Depression in patients with cancer diseases interferes not only with the patient's quality of life but also with the cancer prognosis itself. So diagnosis and treatment of depression in cancer patients is mandatory in most cases [3–5]. Few controlled studies of pharmacological interventions for cancer patients with MD have provided some evidence that antidepressants are effective in reducing depressive symptoms in cancer patients [5–7]. On the other hand, antidepressants used in cancer patients have to face peculiar symptoms related to the disease, such as pain, fatigue, hyporexia, or weight loss. Moreover, such patients have a concomitant multi-pharmacotherapy that should be carefully considered when an antidepressant is chosen. Potential pharmaco-dynamic and pharmaco-kinetic interactions with other agents, the effects of impaired renal, hepatic, or gastro-intestinal functioning on antidepressant metabolism, and side effects which may complicate pre-existing medical conditions should always be considered

[8, 9]. It is therefore very important in the treatment of MD cancer patients to obtain a satisfactory therapeutic response without triggering significant side effects. The class of selective serotonin reuptake inhibitors (SSRIs) has shown it is effective in cancer patients, too [10]. SSRIs may nevertheless cause some transient side effects. Nausea is present in 20–25% of patients, mainly during the first phases of treatment and usually disappears within 1–2 weeks [11–13]. The first weeks are the most critical period for adherence to treatments in all classes of antidepressants. Antidepressant therapy was discontinued by 28% of the patients during the first 30 days after starting therapy, and by 44% within 3 months [14]. Studies on predictors of non-adherence during the starting period of treatment suggested that among the reasons for stopping therapy (poor motivation, hopelessness, lack of perceived relief) [16], the main cause is the emergence of side effects before the improvement of depression. Nausea, although transient, is the most frequent reason for abandoning SSRIs, and it is particularly poorly tolerated by patients undergoing chemotherapy [15, 16]. Another adherence problem is inner tension, which can manifest itself as restlessness [17–19].

In line with these considerations, our study aimed to investigate the tolerability of paroxetine, comparing slower with standard up-titration in a population of cancer patients with depression.

Methods

Patients

The study was approved by the San Giovanni Battista Hospital and University Ethics Committee and all patients gave their written informed consent. All patients were enrolled by the Clinical and Oncological Psychology of University of Turin.

Inclusion criteria are as follows: patients aged 18–75 and suffering from any stage of cancer associated with depression—major depressive disorder (MDD) or dysthymic disorder (DD), or adjustment disorder with depressed mood (ADDM) according to DSM IV TR [20] and with a Montgomery Asberg Depression Rating Scale (MADRS) score ≥11 [21].

Exclusion criteria are as follows: a prior history of psychotic disorder, a comorbid Axis-I disorder other than depression (including bipolar mood disorder), any ongoing chemo-therapeutic treatment, the use of any psychoactive drug in the previous 3 months (with the exception of benzodiazepines), a central nervous system cancer diagnosis or cerebral metastases, less than 18 months' life expectancy, and patients in pregnancy or nursing. The demographic and clinical data are reported in Table 1.

Trial design

The study was an open randomized controlled study aimed at comparing tolerability and efficacy of slow versus standard paroxetine up-titration.

The primary outcome measures were the tolerability evaluated by means of the Dosage Record and Treatment Emergent Symptom Scale (DOTES) [22] and the Subjective Side Effects from Medication (SIDE) scales [23]. Tolerability was assessed at the end of the titration period (2 weeks), after 4 weeks, and at the end of the study period. In addition, tolerability was assessed by means of the drop-out rate due to side effects, and by the frequency and severity of side effects as shown with the DOTES and SIDE scales.

The secondary outcome measures were the efficacy of slow versus standard up-titration measured through depression, anxiety, and quality-of-life scales. These assessments were made after 4 weeks and at the end of the study period (8 weeks). Patient with an improvement in the MADRS score equal or higher than 50% in the last visit in comparison to baseline were considered responders.

Fifteen patients were randomly assigned to slow and 15 to standard up-titration.

The patients randomized to slow up-titration started with 2.5 mg/day of paroxetine, increasing the daily dose by 2.5 mg each third day, until 10 mg/day was reached on day 8. On day 9, the dosage was increased to 15 mg/day and from day 11 patients reached the full dose of 20 mg/day.

The patients randomized to standard up-titration started with 10 mg/day of paroxetine and increased the daily dose to 20 mg/day on day 8.

From day 11 to the end of the study (8 weeks), all patients in both treatments received the same daily dose (20 mg/day). This dosage is the most commonly used in trials including depressed cancer patients [24]. This information is listed in Table 2.

Patients that were taking benzodiazepines at the time of the enrolment in the study were allowed to maintain this treatment during the trial, without any increase in the dosage.

At baseline assessment, the demographic and clinical data of each patient were collected through a semi-structured interview, including the subject's main anamnestic, somatic, and psychological features, and all the inclusion and exclusion criteria were reviewed to check the patient's eligibility. Enrolled patients were assessed at baseline (T0), after the titration period (2 weeks), and after 4 (T1) and 8 (T2) weeks, by clinical psychologists (DC and AB) blind to the kind of titration the patients were assigned to. Psychiatric diagnosis was made through the SCID I-DSM IV TR [20].

t1.1 **Table 1** Sample demographic and clinical characteristics

t1.2			Slow up-titration group	Standard up-titration group	All patients	*p* value
t1.3	Age (years)	Mean±SD (*N*)	59.9±11.7 (15)	61.8±10.5 (15)	60.9±10.9 (30)	0.647
t1.4		Median (min–max)	60 (40–78)	64 (43–78)	62 (40–78)	
t1.5	Sex	Female (%)	73.3 (11/15)	66.7 (10/15)	70 (21/30)	0.690
t1.6		Male (%)	26.7 (4/15)	33.3 (5/15)	30 (9/30)	
t1.7	Educational level	Elementary school (%)			10 (3/30)	
t1.8		Junior high school (%)			43.3 (13/30)	
t1.9		High school (%)			26.6 (8/30)	
t1.10		University (%)			20.0 (6/30)	
t1.11	Cancer site	Colon rectal (%)	13.3 (2/15)	26.7 (4/15)	20 (6/30)	0.566
t1.12		Dermatologic (%)	0 (0/15)	6.7 (1/15)	3.3 (1/30)	
t1.13		Hematologic (%)	13.3 (2/15)	6.7 (1/15)	10 (3/30)	
t1.14		Gastric (%)	6.7 (1/15)	0 (0/15)	3.3 (1/30)	
t1.15		Breast (%)	33.3 (5/15)	26.7 (4/15)	30 (9/30)	
t1.16		Lung (%)	26.7 (4/15)	13.3 (2/15)	20 (6/30)	
t1.17		Head & neck (%)	6.7 (1/15)	6.7 (1/15)	6.7 (2/30)	
t1.18		Others (%)	0 (0/15)	13.3 (2/15)	6.7 (2/30)	
t1.19	Cancer state	No active disease (%)	46.7 (7/15)	46.7 (7/15)	46.7 (14/30)	0.881
t1.20		Local active disease (%)	26.7 (4/15)	33.3 (5/15)	30 (9/30)	
t1.21		Metastatic disease (%)	26.7 (4/15)	20 (3/15)	23.3 (7/30)	
t1.22	Surgery	No (%)	40 (6/15)	20 (3/15)	30 (9/30)	0.232
t1.23		Yes (%)	60 (9/15)	80 (12/15)	70 (21/30)	
t1.24	Chemotherapy	No (%)	20 (3/15)	13.3 (2/15)	16.7 (5/30)	0.624
t1.25		Yes (%)	80 (12/15)	86.7 (13/15)	83.3 (25/30)	
t1.26	Radiotherapy	No (%)	53.3 (8/15)	80 (12/15)	66.7 (20/30)	0.121
t1.27		Yes (%)	46.7 (7/15)	20 (3/15)	33.3 (10/30)	
t1.28	Depressive disease DMS-IV TR	Major depression recurrent episode (%)	33.3 (5/15)	26.7 (4/15)	30 (9/30)	0.711
t1.29		Major depression single episode (%)	0 (0/15)	6.7 (1/15)	3.3 (1/30)	
t1.30		Dysthymia	20 (3/15)	13.3 (2/15)	16.7 (5/30)	
t1.31		Adjustment dis. with depressed mood (%)	46.7 (7/15)	53.3 (8/15)	50 (15/30)	

Outcome measures

Primary outcome measures: tolerability

DOTES is a rating scale for measuring the presence and intensity of psychotropic medication side effects. This hetero-evaluating scale assesses the dosage, adverse effects of the clinical treatments, and their possible relationship with the pharmacological treatment [22].

SIDE [23] is a self-evaluating scale for side effects, assessing the severity and treatment correlation of 48 symptoms.

Secondary outcome measures: efficacy

The Hospital Anxiety and Depression Scale (HADS) [25] is a 14-item (rated 0–3) self-report scale widely used in clinical practice [26–28]. The total HADS depression score ranges from 0 (absence of depression) to 21 (severe depression).

The Montgomery Asberg Depression Rating Scale (MADRS) [21] is a semi-structured clinician-rated interview composed of 10 questions rated from 0 to 6 [21] and a total score range 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) [16, 29].

The European Organization for Research and Treatment of Cancer—Quality of Life Questionnaire Core 30 (EORTC QLQ-C 30) is a 30-item self-reporting questionnaire developed to assess the quality of life of cancer patients. It is grouped into five functional subscales (role, physical, cognitive, emotional, and social functioning). In addition, there are three multi-item symptom scales (fatigue, pain, and nausea and vomiting), individual questions concerning

t2.1 **Table 2** Drugs titration arm A and arm B

t2.2 t2.3 Day	ARM A Slow titration	ARM B Standard titration
t2.4 1	2.5 mg (5 gtt)	10 mg (20 gtt)
t2.5 2	2.5 mg (5 gtt)	10 mg (20 gtt)
t2.6 3	5 mg (10 gtt)	10 mg (20 gtt)
t2.7 4	5 mg (10 gtt)	10 mg (20 gtt)
t2.8 5	7.5 mg (15 gtt)	10 mg (20 gtt)
t2.9 6	7.5 mg (15 gtt)	10 mg (20 gtt)
t2.10 7	10 mg (20 gtt)	10 mg (20 gtt)
t2.11 8	10 mg (20 gtt)	20 mg (40 gtt)
t2.12 9	15 mg (30 gtt)	20 mg (40 gtt)
t2.13 10	15 mg (30 gtt)	20 mg (40 gtt)
t2.14 11	20 mg (40 gtt)	20 mg (40 gtt)
t2.15 12	20 mg (40 gtt)	20 mg (40 gtt)
t2.16 13	20 mg (40 gtt)	20 mg (40 gtt)
t2.17 14	20 mg (40 gtt)	20 mg (40 gtt)
t2.18 15	20 mg (40 gtt)	20 mg (40 gtt)

common symptoms in cancer patients, and two questions assessing overall QOL.

The Hamilton Rating Scale for Anxiety (HAM-A) [30] is a rating scale developed to quantify the severity of anxiety symptoms. It consists of 14 items, each defined by a series of symptoms. Each item is rated on a five-point scale, ranging from 0 (not present) to 4 (severe). Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0–56, where <17 indicates mild, 18–24 mild to moderate, and 25–30 moderate to severe anxiety.

The Clinical Global Impression (CGI) is a standardized assessment tool. It allows the clinician to rate the severity of illness, changes over time, and the efficacy of medication, taking into account the patient's clinical condition and the severity of the side effects.

The Patient Global Impression of Improvement (PGI-I) is a self-evaluating scale used to estimate the patient's satisfaction with improvement (seven responses from "very much worse" to "very much better").

Statistical analysis

Patients were assigned to an arm through a Hardware Random Number Generator, and the homogeneity of the sample was verified for age, sex distribution, and initial severity of depressive illness.

All statistical analyses were performed using SAS version 9.1.3 and an intent-to-treat (ITT) approach was used for the primary end point analysis, i.e., all enrolled patients taking at least one dose of medication and having at least one follow-up assessment are included. The LOCF method (last observation carried forward) was employed in order to fill in missing data in the ITT population.

Unless otherwise specified, all statistical tests were two-tailed, with $p < 0.05$ considered statistically significant. The repeated measure ANOVA was used to analyze variation in all emotional scores (T0–T1–T2) through the observational period. Other parameters were compared by means of chi-square test. Responders to MADRS were analyzed by means of the Fisher exact test.

Results

Thirty consecutive patients meeting the inclusion criteria were randomized to slow or standard paroxetine up-titration group (ITT population). Their demographic characteristics are given in Table 1; drugs titration in Table 2.

According to DSM IV-TR, 33.3% of the patients fulfilled the criteria for major depressive disorder (MDD), single (3.3%) or recurrent (30.0%), 16.7% for dysthymic disorder (DD), and 50% for adjustment disorder with depressive mood (ADDM). No significant differences in age, sex distribution, or severity of depression were found between the two groups at T0 (arm A vs. arm B).

Primary outcome measures: tolerability

DOTES

Twenty patients completed the study. Ten patients dropped out within the up-titration period: four (26.7%) from the slow up-titration group, complaining of gastro-intestinal side effects and asthenia, and six (40%) from the standard titration group, due to restlessness and gastro-intestinal side effects. No significant difference in dropout rates was observed between the groups (p=0.232) (see Fig. 1, consort diagram).

At the end of the titration period (week 2), the hetero-evaluating scale DOTES showed a significant lower rate of patients with side effects in the slow up-titration than in the standard titration group (p=0.013). Of the eight patients with no side effects, seven were in arm A and one in arm B. The number of patients without side effects after T2 and T3 increased to 12/15 in arm A and 8/15 in arm B, respectively (p=0.12) (see Table 3).

The majority (93.3%) of arm B patients (14/15) presented at least one side effect, while only 53.3% of arm A patients did so (8/15).

The quality of side effects was similar in the two groups (arm A vs. arm B—gastro-intestinal disorders 37.5% vs. 28.6%; asthenia 25.0% vs. 7.1%; nausea 12.5% vs. 21.4%). Moreover, 35.7% of patients in arm B demonstrated restlessness versus 12.5% in arm A.

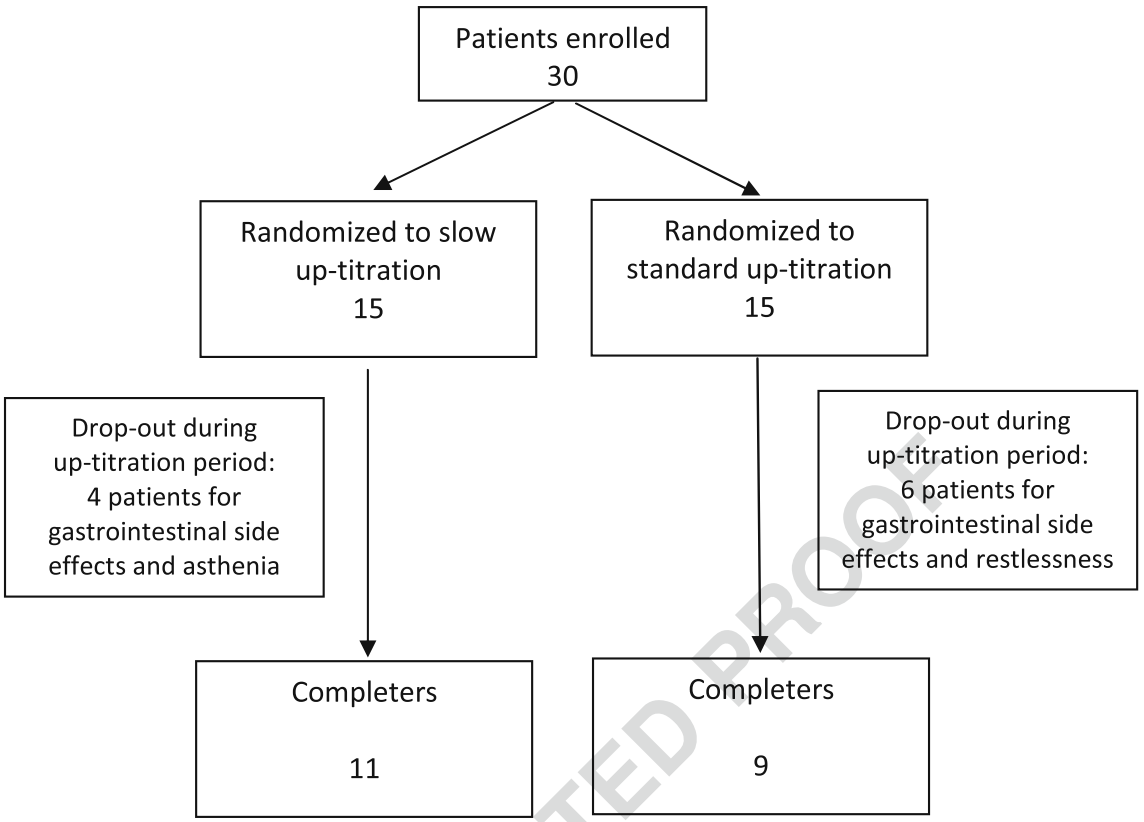

Fig. 1 Consort diagram of the study Q2

The only significant differences between the two groups emerged after 2 weeks: patients with slow titration treatment showed a significantly lower number of severe side effects. The Dotes Severity score demonstrated that the slow up-titration was associated with mild side effects in 33.3% (5/15) of patients, and moderate–severe side effects in 20% (3/15). In the standard titration group, 20% (3/15) of patients presented mild side effects while 73% (11/15) presented side effects classified as moderate–severe. These proportions of patients between the two groups were

t3.1 **Table 3** Patients complaining possible or probable side effects (DOTES and SIDE scales) after the titration period (week 2)

t3.2		DOTES scale	Slow up-titration group	Standard up-titration group	All patients	Diff. (95% CI)	*p* value
t3.3	Week 2	Patients with side effects (%)	53.3 (8/15)	93.3 (14/15)	73.3 (22/30)	−40 (−68.2, −11.8)	0.013
t3.4		Patients without side effects (%)	46.7 (7/15)	6.7 (1/15)	26.7 (8/30)		
t3.5	Week 2—DOTES	Arm A	Arm B	All patients	Difference (95% CI)	*p* value	
t3.6	Severity score						
t3.7	Mild	33.3% (5/15)	20% (3/15)		ND	0.04453	
t3.8	Moderate–severe	20% (3/15)	73% (11/15)		ND		
t3.9	Dotes—relationship						
t3.10	Yes	53.3 (8/15)	93.3 (14/15)	73.3 (22/30)	−40 (−68.2÷−11.8)	0.01324	
t3.11	No	46.7 (7/15)	6.7 (1/15)	26.7 (8/30)			
t3.12		SIDE scale	Slow up-titration group	Standard up-titration group	All patients	Diff. (95% CI)	*p* value
t3.13	Week 2	Patients with side effects (%)	46.7 (7/15)	93.3 (14/15)	70.0 (21/30)	−46.7 (−74.9, −18.4)	0.005
t3.14		Patients without side effects (%)	53.3 (8/15)	6.7 (1/15)	30.0 (9/30)		

statistically significant ($p<0.01$). These data are detailed in Table 3.

SIDE

When the presence of drug-related side effects were evaluated with the self-evaluation scale SIDE at the end of titration period (week 2), 8/15 patients in the slow and 1/15 in the standard up-titration group did not complain of side effects. The rate of patients with side effects after 2 weeks was 46.7% lower in the slow titration group ($p=0.005$). After 4 weeks, and at the end of the treatment, the number of patients with related side effects was not statistically different between the two groups ($p=0.70$).

According to the self-evaluating scale for side effects (SIDE), 46.7% of slow-titrated patients perceived side effects, compared to 93.3% of standard-titrated patients. No differences were found between the two groups (see Table 3).

The difference between the groups on the self-evaluated side effect scale (SIDE) is most interesting: only 9.3% of arm A patients vs. 46.0% of arm B patients complained of bothersome symptoms.

Clinical global impression

Secondary efficacy analyses also showed a global improvement at endpoint in the two groups on the scores of CGI, with no differences between arms after 8 weeks.

After 4 weeks of treatment, the CGI-Side effects score showed significant less interference of side effects in slow-titrated patients in comparison to those on standard titration ($p=0.001$). In arm A, the CGI-Therapeutic effect score was significantly better than in arm B ($p=0.039$) and statistically less interaction of side effects on efficacy was also found ($p=0.023$). The effectiveness—the balance between efficacy (therapeutic effects) and tolerability (side effect)—was significantly higher in arm A than in arm B ($p=0.02$).

No significant difference was found between the two titration groups at the end of treatment. These data are listed in Table 4.

Mood depression

Responders were generally defined as patients with a decrease of at least 50% in the MADRS total score after 3 weeks of therapy. At the end of our study, 46.7% of the patients (14/30) were considered responders in the ITT population, according to the MADRS score improvement. Considering only the patients who completed the study, the MADRS score changes highlighted the following percentages: 10 out of 11 patients (90.1%) in the slow titration and four out of nine (44.4%) in the standard titration group were considered responders ($p<0.06$). As far as the 20 completers were concerned, the MADRS scores in the s severity low up-titration group

Table 4 CGI: side effects and balance between efficacy (therapeutic effects) and tolerability (side effects)

Variable	ARM A	ARM B	All patients	Difference (95% CI)	*p* value
CGI side effects					
Week 4					
Mean±SD (*N*)	1.18±0.4 (11)	2.44±1.01 (9)	1.75±0.97 (20)	−1.26 (−1.96, −0.56)	0.0013
Median (min–max)	1 (1–2)	3 (1–4)	1 (1–4)		
Week 8					
Mean±SD (*N*)	1.45±0.69 (11)	1.33±0.5 (9)	1.4±0.6 (20)	0.12 (−0.46, 0.7)	0.6644
Median (min–max)	1 (1–3)	1 (1–2)	1 (1–3)		
CGI therapeutic effect					
Week 4					
Mean±SD (*N*)	3.27±0.79 (11)	2.44±0.88 (9)	2.9±0.91 (20)	0.83 (0.04, 1.61)	0.0395
Median (min–max)	3 (2–4)	2 (1–4)	3 (1–4)		
Week 8					
Mean±SD (*N*)	3.09±0.94 (11)	2.78±1.2 (9)	2.95±1.05 (20)	0.31 (−0.69, 1.32)	0.5218
Median (min–max)	3 (1–4)	3 (1–4)	3 (1–4)		
CGI efficacy index					
Week 4					
Mean±SD (*N*)	4.09±3.24 (11)	8.33±4.39 (9)	6±4.28 (20)	−4.24 (−7.82, −0.66)	0.0228
Median (min–max)	5 (1–10)	7 (1–16)	5 (1–16)		
Week 8					
Mean±SD (*N*)	5.09±4.09 (11)	6.78±4.47 (9)	5.85±4.23 (20)	−1.69 (−5.71, 2.33)	0.3898
Median (min–max)	5 (1–14)	6 (1–13)	5 (1–14)		

improved from 27.9±7.0 at baseline to 10.2±6.9 at 8 weeks ($p<0.001$), while the MADRS scores in the standard up-titration group improved from 30.7±9.1 at baseline to 16.11±7.8 at 8 weeks ($p<0.001$). After 4 weeks of treatment, the patients with slow up-titration reached a significantly lower MADRS total score in comparison to patients with standard titration ($p<0.01$).

In addition, the HADS score of depression improved significantly in the two groups between T0 and the end point, in both arm A ($p<0.001$) and arm B ($p<0.01$). The HADS self-evaluation was significantly lower in the slow titration than in the standard titration group, both after 4 weeks ($p<0.04$) and 8 weeks of treatment ($p<0.02$) (see Table 5).

Anxiety

The HAM-A improved in both groups, without differences between arms, from baseline to 8 weeks. The HADS self-evaluation score of anxiety score significantly improved in the slow titration compared to the standard up-titration group both at 4 weeks ($p<0.004$) and at the end of the study ($p<0.02$) (see Table 5).

Quality of life

Quality of life (QoL), measured by EORTC QLQ-C30 at week 8, globally improved from baseline without differences between arms (from 54.5±19.2 to 68.5±12.8).

After 4 weeks, the EORTC QLQ-C30 subscales demonstrated a significantly higher improvement in physical functioning ($p<0.0001$), role ($p<0.0004$) and emotional functioning ($p<0.003$), and fatigue ($p<0.0007$) in the slow up-titrated patients compared to the standard titrated ones.

Global health appeared better in the slow up-titration compared to the standard titrated group (70.1±7.7 vs. 53.9±17.2), but the same difference was present at baseline (62.9±10.5 vs. 50.4±19.4). These data are listed in Table 6.

Discussion

A new systematic review by Cochrane researchers at King's Health Partners Academic Health Sciences Centre in the UK suggests that physically ill patients may benefit from pharmacological treatments of depression [31]. Researchers found that drugs were more effective than placebos in the treatment of depression in these patients [31].

In the systematic review carried out by Williams and Dale [32] concerning the effectiveness of treatment for depression/depressive symptoms in adult cancer patients, six studies were randomized placebo controlled trials, four conducted in the USA [24, 33–35] and two in Europe [36, 37]. Only three of these controlled trials reported the antidepressant efficacy of the mood treatment in terms of caseness for depression: one with fluoxetine [39] and two with paroxetine [21, 22, 24–34]. A few other uncontrolled studies have been published concerning the use of paroxetine: in comparison with amitriptyline in breast cancer [38], in the treatment of hot flashes in breast cancer [39], in cancer patients with hematological malignancy [40], and during chemotherapy [35].

However, antidepressants continue to be associated with a significant burden of side effects that affect treatment adherence and quality of life. For this reason, slow titration may be needed to reduce the impact of side effects. According to this consideration, a slow titration could be advantageous to ameliorate effectiveness, resulting from the balance between efficacy and safety. The availability of oral solutions could allow a more flexible dosage, useful during titration periods.

In the present study, we treated 30 depressed cancer patients with paroxetine at 20 mg/day in a single-blind two-arm trial over 8 weeks, comparing two different drug titrations.

As far as pharmacokinetics' properties of paroxetine are concerned, this drug is well absorbed after oral administration and is principally metabolized by CYP2D6 at low concentration even though it inhibits this enzyme in a

Table 5 Emotional evaluation

			Slow up-titration group	Standard up-titration group	All patients	*p* value
HADS anxiety	Baseline	Mean±SD (*N*)	14.0±1.8 (15)	14.3±4.5 (15)	14.2±3.4 (30)	0.793
	Week 4	Mean±SD (*N*)	6.8±2.3 (11)	11.6±4.2 (9)	9.0±4.0 (20)	0.005
	Week 8	Mean±SD (*N*)	6.6±2.8 (11)	9.8±3.0 (9)	8.1±3.2 (20)	0.025
HADS depression	Baseline	Mean±SD (*N*)	12.5±2.7 (15)	14.2±3.8 (15)	13.3±3.4 (30)	0.160
	Week 4	Mean±SD (*N*)	8.3±3.4 (11)	12.2±4.8 (9)	10.0±4.0 (20)	0.045
	Week 8	Mean±SD (*N*)	5.3±3.2 (11)	10.0±5.1 (9)	7.4±4.7 (20)	0.020
MADRS total score	Baseline	Mean±SD (*N*)	27.9±7.0 (15)	30.7±9.1 (15)	29.3±8.1 (30)	0.353
	Week 4	Mean±SD (*N*)	11.3±5.0 (11)	21.7±11.0 (9)	16.0±10.0 (20)	0.011
	Week 8	Mean±SD (*N*)	10.2±7.0 (11)	16.1±7.9 (9)	12.9±7.8 (20)	0.090

t6.1 **Table 6** Quality of Life (EORTC QLQ-C30)

t6.2 Variable	Arm A	Arm B	All patients	*p* value
t6.3 Physical functioning				
t6.4 Week 4				
t6.5 Mean±SD (*N*)	66.82±6.81 (11)	43.89±12.94 (9)	56.5±15.23 (20)	0.0001
t6.6 Median (min–max)	70 (50–75)	45 (25–65)	62.5 (25–75)	
t6.7 Role functioning				
t6.8 Week 4				
t6.9 Mean±SD (*N*)	65.91±12.61 (11)	34.72±19.54 (9)	51.88±22.31 (20)	0.0004
t6.10 Median (min–max)	75 (50–75)	25 (0–62.5)	50 (0–75)	
t6.11 Week 8				
t6.12 Mean±SD (*N*)	60.23±16.6 (11)	38.89±11.6 (9)	50.63±17.9 (20)	0.0044
t6.13 Median (min–max)	62.5 (25–75)	37.5 (25–50)	50 (25–75)	
t6.14 Emotional functioning				
t6.15 Week 4				
t6.16 Mean±SD (*N*)	52.27±5.78 (11)	34.73±16.27 (9)	44.38±14.46 (20)	0.0036
t6.17 Median (min–max)	50 (50–68.75)	37.5 (12.5–56.25)	50 (12.5–68.75)	
t6.18 Social functioning				
t6.19 Week 8				
t6.20 Mean±SD (*N*)	62.5±11.18 (11)	50±13.98 (9)	56.88±13.74 (20)	0.0391
t6.21 Median (min–max)	62.5 (50–75)	50 (25–75)	50 (25–75)	
t6.22 Global health				
t6.23 Week 0				
t6.24 Mean±SD (*N*)	62.85±10.52 (15)	50.45±19.38 (15)	56.65±16.57 (30)	0.0380
t6.25 Median (min–max)	57.14 (42.85–85.71)	42.85 (14.2–85.71)	57.14 (14.2–85.71)	
t6.26 Week 4				
t6.27 Mean±SD (N)	70.11±7.7 (11)	53.93±17.19 (9)	62.83±14.96 (20)	0.0116
t6.28 Median (min–max)	71.4 (57.14–85.71)	57.1 (28.5–85.71)	71.4 (28.5–85.71)	

concentration-dependent manner. The kinetic information indicates that paroxetine is metabolized by more than one enzyme. Two contribution components were distinguished: one with high affinity and readily saturable, the other with low affinity [41]. The relative roles of two enzymes in the metabolism of paroxetine is the apparent explanation for why paroxetine has non-linear pharmacokinetics including a half-life of 10 h after a single 20-mg dose, but a half-life of almost 24 h after multiple doses of 20 mg/day [42]. Steady-state concentration occurs after about 10 days of treatment for most adults, but it may take substantially longer in an occasional patient. The metabolites are primarily excreted in urine and to some extent in the feces. Paroxetine is equally bioavailable from liquid suspension and tablets.

With regard to the efficacy parameters, at the end of our study 46.7% of whole patient group were considered responders in the ITT population according to the MADRS score improvement. Standard dosage paroxetine was not significantly more effective at achieving a response than low dosage at 8 weeks. Our data confirmed equivalent efficacy between the two arms.

With regard to safety parameters, one patient dropped out because the cancer pathology worsened and nine patients because of side effects: in arm A, two patients dropped out because of gastro-intestinal side effects, and one because of dizziness and sub-confusion; in arm B, four patients dropped out because of restlessness and tremors, and two because of gastro-intestinal side effects (global drop-out rate ten patients). Previous studies with paroxetine in depressed cancer patients reported a drop-out rate from 25% [34] to 55.8% (48.2% because of side effects) [41].

The majority of side effects appeared within the first 2 weeks of treatment: 8/15 patients in arm A showed side effects, mild in five patients (62.5%), and moderate–severe in three (37.5%). In the standard titration group, 14/15 patients showed side effects, three patients (21.4%) presented mild side effects, and in 11 patients (78.6%) the side effects were classified as moderate–severe.

It is well known that most patients discontinue antidepressant treatment for several reasons, such as poor motivation regarding treatment (perhaps related to low awareness), hopelessness (concerning the possible effectiveness of a drug treatment), and lack of perceived relief (particularly because side effects usually appeared before mood improvement) [16].

As a matter of fact, the main cause of discontinuation in the first phase of treatment is the emergence of side effects.

Sensitivity to side effects, and consequently the probability of dropping out, is closely connected both to severity of the side effects and to the patients' subjective perception. In this respect, patients with MD usually show high sensitivity to side effects since the neurotransmitter deficit induces a post-synaptic receptor up-regulation. For example, when a rapid 5HT increase is induced by SSRIs, the systemic 5HT response is amplified, with a transient increase of side effects until the serotonergic system is down-regulated [11]. So slow titration of an SSRI can gradually increase the synaptic concentration of 5HT, reducing the side effects related to the first period of up-regulation, until the therapeutic synaptic down-regulation is achieved.

In this study, the side effects were both hetero-evaluated (DOTES) and self-evaluated (SIDE). In arm A (slow titration), eight patients (53.3%) demonstrated at least one side effect of slight–moderate intensity (mainly gastro-intestinal), while severe side effects were found in only two patients. In arm B (standard titration), 14 patients (93.3%) presented at least one side effect to DOTES, slight–moderate in 10 patients (71.5%) but severe in four patients (28.5%).

Interestingly, in arm B restlessness was present after 15 days in 35.7% of patients, while in arm A the same side effect was limited to 12.5% of patients. In our experience, such a symptom is closely connected to low compliance because of its great interference with the general well-being of the patient.

The side effects of SSRIs are not usually long lasting, but decrease after a few weeks of treatment (probably due to the synaptic down-regulation)[11]: in the present study, the global number of patients without side effects increased in the course of the follow-up, with an absence in both groups of severe side effects at T2.

When the self-evaluating results on the scale for side effects (SIDE) were compared, 46.7% patients (7/15) in arm A perceived side effects after 15 days compared to 93.3% of patients (14/15) in arm B. This result is noteworthy as it is related to self-perception of therapeutic discomfort, which is linked to a balance between efficacy and tolerance of the treatment. Patients with slow titration, apart from pharmacological considerations, are more reassured by a slow increase in dosage. Cancer patients are actually more sensitive to side effects because their long history of disease and treatment induces increased negative expectations of adverse pharmacological events.

The main limitation of our study is the small sample size, which limits the possibility of generalizing the results. This pilot study may nevertheless arouse interest in the question of compliance related to the management of the side effects of SSRIs treatment. Despite their safety and tolerability with respect to tricyclic antidepressants [43], these drugs cause side effects in the first phase of the treatment, so proper management of such a delicate period would allow a higher number of patients to continue with the antidepressant treatment, particularly in a frail population such as cancer patients.

Conclusion

This study aimed to compare two different paroxetine titrations (slow versus standard) in the treatment of depression in cancer patients. As far as tolerability is concerned, the results suggest that slow titration can reduce the number and severity of side effects, thus reducing the drug-related drop-out compared to standard titration. In addition, slow titration was found to be as effective as standard titration: both titrations groups highlighted a significant improvement of depression, anxiety, and quality-of-life measures.

In conclusion, the results of this study confirm previous evidence on the efficacy and safety of paroxetine in the treatment of depressed cancer patients [38–44]. Going further than previous studies, our results suggest that slow titration is better tolerated than standard paroxetine titration for the treatment of depression in cancer patients. Further controlled trials are needed to confirm this evidence.

Conflict of interest None declared.

We state that we have full control of all primary data and we agree to allow the journal to review our data if requested.

References

1. Spiegel D, Giese-Davis J (2003) Depression and cancer: mechanisms and disease progression. Biol Psychiatry 54 (3):269–282
2. Hamer M, Chida Y, Molloy GJ (2009) Psychological distress and cancer mortality. J Psychosom Res 66(3):255–258, Epub 2009 Jan 16
3. Smith E, Gomm S, Dickens C (2003) Assessing the independent contribution to quality of life from anxiety and depression in patients with advanced cancer. Palliat Med 17(6):509–513
4. Massie MJ (2004) Prevalence of depression in patients with cancer. J Natl Cancer Inst Monogr 2004(32):57–71
5. Pirl WF (2004) Evidence report on the occurrence, assessment, and treatment of depression in cancer patients. J Natl Cancer Inst Monogr (32):32–39
6. Angelino AF, Treisman GJ (2001) Major depression and demoralization in cancer patients: diagnostic and treatment considerations. Support Care Cancer 9(5):344–349
7. Rodin G, Lloyd N, Katz M, Green E, Mackay JA, Wong RK (2007) The treatment of depression in cancer patients: a systematic review. Support Care Cancer 15(2):123–136, Epub 2006 Oct 21
8. Strong V, Waters R, Hibberd C, Murray G, Wall L, Walker J, McHugh G, Walker A, Sharpe M (2008) Management of

depression for people with cancer (SMaRT oncology 1): a randomised trial. Lancet 372(9632):40–48
9. Torta R, Siri I, Caldera P (2008) Sertraline effectiveness and safety in depressed oncological patients. Support Care Cancer 16 (1):83–91, Epub 2007 Sep 14
10. Rodin G (2008) Treatment of depression in patients with cancer. Lancet 372(9632):8–10
11. Bull SA, Hu XH, Hunkeler EM et al (2002) Discontinuation of use and switching of antidepressants: influence of patient–physician communication. JAMA 288:1403–1409
12. Beasley CM Jr, Koke SC, Nilsson ME, Gonzales JS (2000) Adverse events and treatment discontinuations in clinical trials of fluoxetine in major depressive disorder: an updated meta-analysis. Clin Ther 22:1319–1330
13. Kobak KA, Taylor L, Katzelnick DJ et al (2002) Antidepressant medication management and Health Plan Employer Data Information Set (HEDIS) criteria: reasons for nonadherence. J Clin Psychiatry 63:727–732
14. Masand PS (2003) Tolerability and adherence issues in antidepressant therapy. Clin Ther 25(8):2289–2304
15. Young AS, Klap R, Sherbourne CD, Wells KB (2001) The quality of care for depressive and anxiety disorders in the United States. Arch Gen Psychiatry 58:55–61
16. Rosholm JU, Andersen M, Gram LF (2001) Are there differences in the use of selective serotonin reuptake inhibitors and tricyclic antidepressants? A prescription database study. Eur J Clin Pharmacol 56:923–929
17. Onishi H, Yamamoto W, Wada M, Nishida T et al (2007) Detection and treatment of akathisia in advanced cancer patients during adjuvant analgesic therapy with tricyclic antidepressants: case reports and review of the literature. Palliat Support Care 5(4):411–414
18. Sinclair LI, Christmas DM, Hood SD, Potokar JP et al (2009) Antidepressant-induced jitteriness/anxiety syndrome: systematic review. Br J Psychiatry 194(6):483–490
19. Barbui C, Hotopf M, Freemantle N, Boynton J et al (2007) WITHDRAWN: treatment discontinuation with selective serotonin reuptake inhibitors (SSRIs) versus tricyclic antidepressants (TCAs). Cochrane Database Syst Rev 18(3):CD002791
20. American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders, fourth edition, text revision. American Psychiatric Association, Washington
21. Montgomery SA, Asberg M (1979) A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389
Q3 22. (1976) DOTES: dosage record and treatment emergent symptom scale. In: Rockville GW (ed) ECDEU assessment manual for psychopharmacology, rev. ed. National Institute of Mental Health
Q4 23. Weiden, Zygmunt (1999) Subjective side effects from medication
24. Musselman DL, Lawson DH, Gumnick JF, Manatunga AK et al (2001) Paroxetine for the prevention of depression induced by high-dose interferon alfa. N Engl J Med 344:961–966
25. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361–370
26. Kearns NP, Cruickshank CA, McGuigan KJ, Riley SA, Shaw SP, Snaith RP (1982) A comparison of depression rating scales. Br J Psychiatry 141:45–49
27. Zimmerman M, Posternak MA, Chelminski I (2004) Implications of using different cut-offs on symptom severity scales to define remission from depression. Int Clin Psychopharmacol 19(4):215–220
28. Costantini M, Musso M, Viterbori P, Bonci F, Del Mastro L, Garrone O, Venturini M, Morasso G (1999) Detecting psychological distress in cancer patients: validity of the Italian version of the hospital anxiety and depression scale. Support Care Cancer 7 (3):121–127
29. Zimmerman M, Posternak MA, Chelminski I (2004) Derivation of a definition of remission on the Montgomery–Asberg depression rating scale corresponding to the definition of remission on the Hamilton rating scale for depression. J Psychiatr Res 38(6):577–582
30. Hamilton M (1959) The assessment of anxiety states by rating. Br J Med Psychol 32:50–55
31. Rayner L, Price A, Evans A, Valsraj K, Higginson IJ, Hotopf M (2010) Antidepressants for depression in physically ill people. Cochrane Database Syst Rev (3):CD007503. doi:10.1002/14651858.CD007503.pub2
32. Williams S, Dale J (2006) The effectiveness of treatment for depression/depressive symptoms in adults with cancer: a systematic review. Br J Cancer 94:372–390
33. Fisch MJ, Loehrer PJ, Kristeller J, Passik S et al (2003) Fluoxetine versus placebo in advanced cancer outpatients: a double-blinded trial of the Hoosier oncology group. J Clin Oncol 21:1937–1943
34. Morrow GR, Hickok JT, Roscoe JA, Raubertas RF et al (2003) Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the University of Rochester Cancer Center Community Clinical Oncology Program. J Clin Oncol 21:4635–4641
35. Roscoe JA, Morrow GR, Hickok JT, Mustian KM et al (2005) Effect of paroxetine hydrochloride (Paxil) on fatigue and depression in breast cancer patients receiving chemotherapy. Breast Cancer Res Treat 89:243–249
36. Razavi D, Allilaire JF, Smith M, Salimpour A, Verra M et al (1996) The effect of fluoxetine on anxiety and depression symptoms in cancer patients. Acta Psychiatr Scand 94:205–210
37. Van Heeringen K, Zivkov M (1996) Pharmacological treatment of depression in cancer patients. A placebo-controlled study of mianserin. Br J Psychiatry 169:440–443
38. Pezzella G, Moslinger-Gehmayr R, Contu A (2001) Treatment of depression in patients with breast cancer: a comparison between paroxetine and amitriptyline. Breast Cancer Res Treat 70(1):1–10
39. Weitzner MA, Moncello J, Jacobsen PB, Minton SJ (2002) A pilot trial of paroxetine for the treatment of hot flashes and associated symptoms in women with breast cancer. Pain Symptom Manage 23(4):337–345
40. Chi-Un P, Kim Y-J, Won W-Y, Kim H-J et al (2004) Paroxetine in the treatment of depressed patients with haematological malignancy: an open-label study. Hum Psychopharmacol Clin Exp 19-1:25–29
41. Bloomer JC, Woods FR, Haddock RE, Lennard MS, Tucker T (1992) The role of cytochrome P4502D6 in the metabolism of paroxetine by human liver microsomes. Br J Clin Pharmacol 33:521–523
42. Kaye CM, Haddock RE, Langley PF et al (1989) A review of the metabolism and pharmacokinetics of paroxetine in man. Acta Psychiatr Scand 80(350):60–75
43. Wagstaff AJ, Cheer SM, Matheson AJ, Ormrod D, Goa Kl (2002) Paroxetine: an update of its use in psychiatric disorders in adults. Drugs 62:655–703
44. Musselman DL, Somerset WI, Guo Y, Manatunga AK et al (2006) A double-blind, multicenter, parallel-group study of paroxetine, desipramine, or placebo in breast cancer patients (stages I, II, III, and IV) with major depression. J Clin Psychiatry 67(2):288–296

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES.

Q1. Tables were renumbered. Original citation was Tables 1, 2, 3, 4, 5, 6, and 7 Please check if appropriate.
Q2. Table 3 (not tabular in form) was changed to Fig. 1. Please check if appropriate.
Q3. Please provide complete bibliographic information (authors names and publisher location) for reference no. 22.
Q4. Please provide complete bibliographic information (first name initials for the authors Weiden and Zygmunt and publisher name and location) for reference no. 23.