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Clinical Study on the Efficacy and Safety of Fluvoxamine Treatment for the Tumor Related Depressive Status

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Clinical Study on the Efficacy and Safety of Fluvoxamine Treatment for the Tumor Related Depressive Status

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Results: 101 patients from 7 different centers in China participated in this study. After eight-week treatment, the HAMD-17 score (10.9vs.23.2, $P<0.001$) and HAMA score (10.8 vs. 22.8, $P<0.001$) dropped significantly compared with baseline. The total score of MOS-SS (49.4 vs. 34.9, $P<0.001$), together with the scores of all 6 dimensions, were improved significantly. No serious adverse events related to fluvoxamine were observed, and no statistical difference between the low dose (50-100 mg daily) and medium/ highdose (more than 100 mg daily) groups (14.5% vs. 8.7%, $P=0.366$).

Conclusion: Our results are promising and preliminarily support that fluvoxamine is safe and could alleviate depressive and anxious symptoms and improve the sleep quality of cancer patients with moderate to severe depressive disorder.

Keywords: depressive disorder, cancer, fluvoxamine, anxiety, sleep-quality.

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I. Introduction

Cancer, along with adverse reactions of its treatments, not only impair patients' physical health but also put patients' families in a severe economic crisis. Reports show that about 20% of cancer patients suffer from depressive disorder, and about 15% of cancer patients are subjected to major depressive disorder (MDD)[1]. Cancer accompanied by the depressive disorder vitiates the patients' quality of life[2, 3], hinders the treatment efficacy[4], prolongs the hospitalization time[5], brings a tremendous economic burden to family and society[6], and ultimately increase the suicidal risk of cancer patients. Recent reports showed that depressive disorder was an independent risk factor for cancer mortality[7, 8]. Cancer patients with depressive symptoms have a 26% higher mortality rate than those without depressive symptoms, and those diagnosed with MDD have a 39% higher mortality rate than those without the MDD[9]. The depressive disorder includes a variety of symptoms, including anxiety and sleep disruption[10]. However, the mental health of cancer patients is seldom got enough concern from the health workers. In recent years, Chinese clinicians became aware of this phenomenon. They developed the concept of tumor-related depressive disorder (TRDD), which can be illustrated as a group of depressive symptoms or depressive status rather than psychiatric depression. They also advocate that patients with severe TRDD should be treated with psychiatric medication interventions.

Antidepressants were reported to be beneficial to managing both depressive and anxious symptoms in adult cancer patients[11-13]. Selective serotonin reuptake inhibitors (SSRIs) have efficacy in improving depression in patients with cancer in randomized controlled trials (RCTs)[14, 15]. They are recommended to moderate to severe depressive disorder management in the National Comprehensive Cancer Network (NCCN) guidelines [10, 16]. Fluvoxamine is one of the SSRIs widely used for

depressive disorder, obsessive-compulsive disorder, and anxiety[17]. Fluvoxamine was proved effective in moderate major depression[18]. Meanwhile, an open-label, baseline-controlled study indicated that fluvoxamine could improve polysomnography parameters and simultaneously ameliorate insomnia complaints during the 8-weektreatment [19]. Its efficacy was comparable with other SSRI drugs[19].

Many researchers demonstrated that SSRIs effectively improved depressive disorder in cancer patients. However, whether fluvoxamine is beneficial in treating the depressive disorder and sleep quality in cancer patients remains unclear. Therefore, this study was designed to evaluate the efficacy and safety of fluvoxamine in treating depressive disorder, anxiety, and sleep quality for cancer patients with moderate to severe depressive disorder.

II. Methods

a) Patients and Study Design

This study was a multicenter clinical trial. Patients were recruited from 7 cancer specialists or general hospitals in China, including Tongji Hospital of Huazhong University of science and technology, the first affiliated Hospital of Guangzhou medical University, affiliated tumor Hospital of Xinjiang medical University, Xuzhou central Hospital, Shandong cancer Hospital, Shanxi provincial people's Hospital, and the second affiliated Hospital of Xinjiang medical University.

This study was approved by the ethics committee of Tongji hospital of Huazhong University of Science and Technology (Approval Number by CFDA: 2015R006398), and it was registered in Chinese Clinical Trial Registry (Registration number: ChiCTR20000 30498).

Patients who met all the following inclusion criteria were eligible to participate in the study: (a) age between 18 and 75 years, (b) histological or cytological diagnosis of cancer, (c) life expectancy more than six months, (d) diagnosed as depressive disorder by psychiatrists according to the Guidelines for the Management of Depressive Disorder with ICD-10, (e) Scale for Depression (17 items) (HRSD-17) score≥ 18[20], (f) agreed to participate in this study and signed the Informed Consent Form.

Patients who met one or more following exclusion criteria were excluded: (a) barriers to communication, (b) cognitive dysfunction, (c) aware of cancer diagnosed less than one month, (d) central nervous system (CNS) involved, (e) pregnant or breastfeeding, (f) hypersensitivity to fluvoxamine or its components, (g) with high suicide risk, (h) with a severe and uncontrolled medical condition that would affect patients' compliance or obscure the interpretation of toxicity or adverse events, (i) history of seizures, (j) participated in other drug clinical trials within four weeks, (k) treated with antidepressants within two weeks, (l)unsupervised or unable to take medicine as prescribed.

The study protocol flowchart is shown in Figure 1. All eligible patients were enrolled in the study with a unique code after signing the informed consent. Baseline data were collected by investigators before the patients started the treatment with fluvoxamine maleate (Livzon pharmaceutical group inc. China).In the dose adjustment period (week 1), fluvoxamine maleate was administered with an initial dose of 50 mg for 2 or 3 days, and was gradually added to the effective dose, once a day, after dinner (large dose can be divided into the morning and evening doses),the total daily dose for moderate depression is 100-150 mg and 200-300 mg for major depression. The suggested effective dose was 100 mg to 150 mg daily. In the dose maintenance period (week 2 to 8), fluvoxamine maleate was administered at the same dose as the end of week 1. Related treatments were performed, or the dosage was reduced by 50 mg an intolerable adverse reaction.

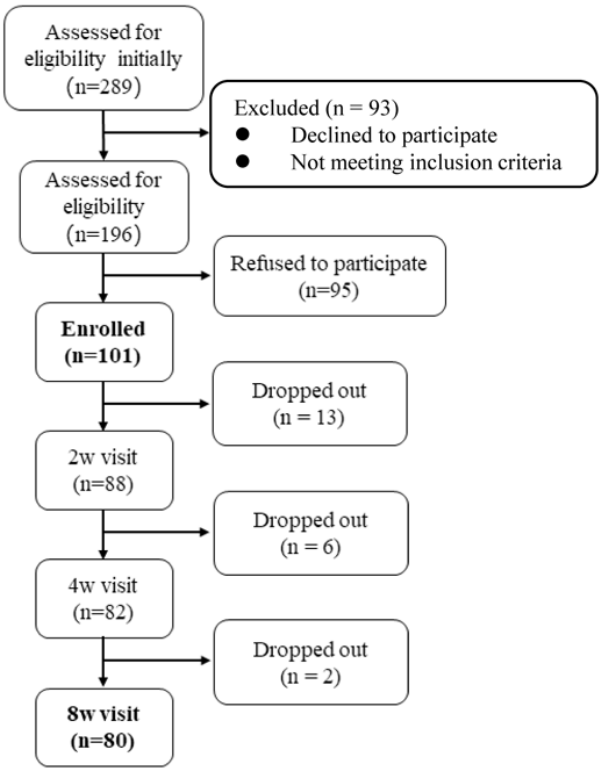

Figure 1: Study protocol and flowchart

b) Data collection and follow-up processes

Before treatment, baseline information, including demographic data, medical history, physical examination data, laboratory examination data, mental status, and sleep quality, was collected. Blood routine examination, blood biochemical examination, electrocardiogram, HAMD-17 (Hamilton Depression Rating Scale), HAMA (Hamilton Anxiety Scale), and MOS-SS (Medical Outcomes Study Sleep Scale) were assessed by qualified raters at baseline and on weeks 2, 4, and 8 during the treatment. All the raters were well trained and had excellent interrater reliability. The investigator gave fluvoxamine treatment based on the clinical manifestation that the doctor determined. The investigator did not interfere with the anti-tumor treatment of cancer patients during their hospitalization.

The laboratory examination data were recorded after eight weeks of treatment. Adverse events were recorded immediately during the study, and the correlation between adverse events and antidepressant treatment was evaluated as soon as possible. Any adverse event related to antidepressant treatment was recorded as an adverse reaction.

c) Outcome measurements

The primary outcome of our study was the response rate after eight weeks of treatment. The reduction of HAMD-17 scores by more than or equal to 50% was defined as a positive response. Secondary outcomes included:

1. the reduction of HAMA scores among baseline on weeks 2, 4, and 8 of treatment,
2. the increase of MOS-SS scores among baseline on weeks 2, 4, and 8 of treatment,
3. the rate of adverse reactions. Subgroup analyses were performed for different ages, tumor stages, and whether chemotherapy was synchronized, and further analyses were performed for outcomes at baseline and 8 weeks of treatment.

d) Statistical analysis

Efficacy analysis was carried out on patients treated with fluvoxamine at least for 2 weeks and completed the post-treatment follow-up. The effect of fluvoxamine treatment was defined by changes from baseline to Week8 in HAMD-17, HAMA, and Sleep Index IIscore. Numerical variables are expressed as mean ± SD. Univariate differences were analyzed using paired t-test among different time points. Safety analysis was carried out on patients treated with fluvoxamine at least once and had a safety evaluation. The qualitative variable was expressed as numbers and percentages. Safety measures were assessed using the chi-square test for differences in groups. SPSS 20.0 software (IBM, Armonk, NY) was used for statistical analysis. $P<0.05$ was considered statistically significant.

III. Results

a) Patients

Demographic characteristics of participants were recorded (Table 1), and psychological states (Table 2) were evaluated at the baseline for all patients. A total of 101 patients from 7 centers in China were included in this study. Among them, 88 (87.1%), 82 (81.2%), and 80 (79.2%) patients completed 2, 4, and 8 weeks of treatments, respectively, with post-treatments follow-ups. In this research, 46 (45.5%) patients were male, 87 (86.1%) patients aged under 65-year-old, patients with lung (36), breast (23), and colorectal (10) cancers predominated among the subjects. Cancer is mainly staged as stage IV (40, 39.6%), primary anticancer treatments are surgery and chemotherapies (27, 26.7%), 27, 74 of them were severe depression and moderate depression. 28, 45, 8 were obvious anxiety, definitely anxiety, possible anxiety.

Table 1: The clinical characteristics of patients at baseline

		N	%
Gender	Male	46	45.5
	Female	55	54.5
Age(years)	<60	66	65.3
	60-65	21	20.8
	>65	14	13.9
Education(years)	<10	56	55.4
	10-12	26	25.7
	>12	19	18.8
Cancer site	Lung	36	35.6
	Breast	23	22.8
	Colon or rectum	10	9.9
	Stomach	7	6.9
	Lymphoma	5	4.9
	Pancreas	3	3.0
	Esophagus	3	3.0
	Cervix	3	3.0
	Other	11	10.9
Cancer stage	I	7	6.9
	II	22	21.8
	III	32	31.7
	IV	40	39.6
Anticancer therapy	Surgery	9	8.9
	Chem	45	44.5
	Radi	3	3.0
	Surg+chem	27	26.7
	Surg+radi	2	2.0
	Radi+chem	6	5.9
	Surg+chem+radi	9	8.9

Surg: surgery; Chem: chemotherapy; Radi: radiotherapy.

Table 2: The psychological characteristics of patients at baseline

		N	%
Depression stage	Severe depression	27	26.7
	Moderate depression	74	73.3
Anxiety stage	Severe anxiety	20	19.8
	Obvious anxiety	28	27.7
	Positive anxiety	45	44.5
	Possible anxiety	8	7.9

Severe depression: HAMD scores >24; Moderate depression: 17 <HAMD scores ≤24.Severe anxiety: HAMA scores >29; Obvious anxiety: 21 <HAMA scores ≤29; Positive anxiety: 14 <HAMA scores ≤21; Possible anxiety: 7 <HAMA scores ≤14.

b) Main evaluation indicators

i. *Outcomes of HAMD-17 score after treatment.*

Eighty patients had completed eight weeks of treatment and the corresponding post-treatment follow-up. After eight weeks treatment with fluvoxamine, the primary evaluation response rate (the reduction rate of HAMD-17 scores≥ 50%) was 58.8% (47/80). The remission (HAMD-17 score decreased to < 7 points) rate was 23.8% (19/80) (Table 3).

Depressive symptoms reduced significantly on week 8 after antidepressant treatment (Table 4). The HAMD-17 score after 8 weeks of treatment with fluvoxamine (10.9±4.8) dropped significantly compared with those at baseline (23.2 ± 4.7) (P< 0.001).

From the results of the subgroup analysis, the rate of HAMD-17 score reduction after fluvoxamine was higher in patients who underwent concurrent chemotherapy than in those who did not. However, there was no statistical difference between the two groups. In contrast, patients younger than 50 had slightly higher scores at baseline, while the rate of score reduction between the two groups after treatment likewise appeared to be different. From the perspective of tumor stage, there was no statistical difference in depression scores between patients with early-stage tumors and those with intermediate and advanced stages, nor was there a statistical difference in the rate of score reduction between the two groups after treatment.

Table 3: The response and remission rate of fluvoxamine treating Cancer patients with moderate to severe depression

Depression stage	N	%	Define
Response	47	58.8	the reduction rate of HAMD scores ≥ 50%
Remission	19	23.8	HAMD scores < 7 points

Table 4: Variation in scores on three scales for fluvoxamine use in cancer patients with moderate to severe depression.

Scale	Time	Baseline ($\bar{x}\pm s$)	Visits ($\bar{x}\pm s$)	Reduction rate (%) ($\bar{x}\pm s$)	N	P-Value
HAMD	8w	23.2 ± 4.7	10.9±4.8	52.6±20.4	80	< 0.0001
HAMA	8w	22.8 ± 6.9	10.8±5.3	51.4±53.6	80	< 0.0001
MOS-SS	8w	34.9 ± 9.1	49.4±11.5	53.7±38.0	80	< 0.0001

HAMD: Hamilton Depression Scale (17 items); SD: Standard Deviation;
HAMA: Hamilton Anxiety Scale; SD: Standard Deviation
MOS-SS: Medical Outcomes Study Sleep Scale

c) *Secondary evaluation indicators*

i. *Outcomes of HAMA score after treatment*

The anxious symptoms scores reduced significantly on weeks 8 after antidepressant treatment compared with those at baseline (Table 5). The HAMA score after eight weeks of treatment with fluvoxamine (10.8±5.3) decreased significantly compared with that at baseline (22.8 ± 6.9) ($P<0.001$).

Table 5: Variations in HAMD score in three aspects after fluvoxamine treating in cancer patients with moderate to severe depression.

Stratification	Item	Baseline (Mean±SD)	Visit3 (Mean±SD)	change rate (%) (Mean±SD)	N	d(95%CI)	[a]*P*-Value
Treatment	Chemotherapy	23.47±4.10	12.23±4.37	-47.08±18.45	51	[9.71,12.76]	<.0001
	Non-Chemotherapy	21.20±3.83	14.60±2.07	-30.21±9.72	29	[2.92,10.28]	0.0076
	[b]*P*-Value	0.2424	0.2403	0.0507			
Age	Year<50	25.57±3.82	13.93±4.38	-44.47±17.43	33	[8.24,15.04]	<.0001
	Year>=50	22.28±3.91	11.85±4.10	-45.93±18.76	47	[8.85,12.02]	<.0001
	[b]*P*-Value	0.0089	0.1154	0.7997			
Cancer Stage	I	25.00±1.41	12.00±4.24	-52.40±14.28	2		
	II	26.25±5.23	10.00±5.24	-62.11±14.70	8	[11.88,20.62]	<.0001
	III	21.29±3.09	12.43±3.99	-40.66±20.77	21	[4.47,13.24]	0.0026
	IV	24.79±3.55	12.42±4.86	-50.20±17.30	49	[10.22,14.52]	<.0001
	[b]*P*-Value	0.1067	0.6681	0.1453			

a, compared with Visit3.

b, compared between each group.

ii. *Outcomes of MOSS-SS score after treatment*

Sleep quality improved significantly on weeks 8 after antidepressant treatment compared with baseline. The MOS-SS score of the cancer patients increased significantly after eight weeks of treatment with fluvoxamine (49.4±11.5) compared with that at baseline (34.9 ± 9.1) ($P<0.001$). After 8 weeks of treatment, not only the total score of MOS-SS, but also the scores of all 6 dimensions were improved significantly, including sleep disturbance (66.6 vs. 40.5, $P<0.001$), adequacy of sleep (69.9 vs. 48.2, $P<0.001$), daytime somnolence (65.2 vs. 50.9, $P<0.001$), snoring (74.6 vs. 62.7, $P<0.001$), shortness of breath after waking up (70.0 vs. 51.3, $P<0.001$), and sleep quantity (75.9 vs. 54.3, $P<0.001$) (Table 6).

Table 6: Fluvoxamine increased all the subtypes of MOS-SS scores in cancer patients with moderate to severe depression.

MOS-SS scores	Baseline ($\bar{x}\pm s$)	After treatment ($\bar{x}\pm s$)	Changes	*P*-Value
Sleep disturbance	40.5 ± 13.3	66.6 ± 23.3	+26.1	< 0.0001
Adequacy of sleep	48.2 ± 15.3	69.9 ± 20.1	+21.7	< 0.0001
Daytime somnolence	50.9 ± 16.4	65.2 ± 18.3	+14.3	< 0.0001
Snoring	62.7 ± 26.2	74.6 ± 20.0	+11.9	< 0.0001
Shortness of breath after waking up	51.3 ± 22.8	70.0 ± 15.8	+18.7	< 0.0001
Sleep quantity	54.3 ± 12.9	75.9 ± 18.5	+21.6	< 0.0001

+: Sleep quality was improved after treatment.

The adverse reactions to fluvoxamine in this study were mild.

The adverse reactions of fluvoxamine in this study were mild, including nausea and vomiting, occasional palpitations, dizziness, and elevated blood pressure. The total ratio of cancer patients with adverse reactions was 11.9%. There was no statistical difference between the low dose (50-100 mg daily) and medium/

highdose (more than 100 mg daily) groups (14.5% vs. 8.7%, P=0.366) (Table 7).

Table 7: Adverse reactions at different doses of fluvoxamine treating cancer patients with moderate to severe depression

	Total	With adverse action	%
Low dose	55	8	14.5
Middle/ High dose	46	4	8.7
χ^2			0.819
P-Value			0.366

IV. Discussion

TRDD is a group of depressive symptoms or depressive status rather than psychiatric depression. TRDD includes depressive disorder, anxiety and sleep disorder. Depressive disorder can cause poor mental and emotional conditions among cancer patients, negatively impacting the quality of life, and lessening the efficacy of anticancer treatment. Improvement in depressive disorder would generally improve the total depressive disorder scores and the subscales measuring anxiety and sleep.

It was reported that antidepressants were beneficial in the depressive treatment in cancer patients. However, the number of randomized, controlled trials of antidepressants on the depressive disorder in cancer patients is limited[11].

Fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), is widely used for depressive disorder and anxiety. Fluvoxamine could be prescribed to patients with MDD and anxiety in Japan and Chinain many countries. Fluvoxamine, a commonly used clinical antidepressant, is associated with Sig-1R, and in vitro studies have shown periodically that it alleviates paclitaxel-induced neurotoxicity and inhibits glioblastoma.

Referring to the Chinese expert consensus on tumor-related depressive states, health education and psychological support can be given to those with mild symptoms, and medication is needed for moderate to severe depressive states. However, most of the medications recommended in the guidelines are herbal tonics, which are not very convenient to take, we designed an initial POC (proof of concept) study to evaluate TRDD in patients before and after fluvoxamine treatment. Our study showed that patients with high post-screening HRSD scores with severe and significant anxiety were 19.8% and 27.7%, respectively. At the same time, patients who completed 8 weeks of pharmacotherapy showed significant improvement not only in depression scores but also in anxiety as measured by the HAMA scale.

A double-blind, randomized, placebo-controlled study reported by Zanardi R showed that the response rate (HAMD-17-21 scores ≤ 8 points, and delusional experience scores (DDERS) = 0 points) of fluvoxamine in treating severe depressive disorder (300 mg daily for 6 weeks) was 78.6%[21]. Besides, a double-blind, randomized, placebo-controlled study reported by Clerc G showed that the response rate of fluvoxamine to treat moderate to severe depressive disorder was 60.7%, the clinical symptom improved by 60.7% (GCI score = 0 or 1), and HAMD-17-17 scores decreased 49.7%[22]. The results reported by Clerc G were similar to previous studies.

Our findings showed similar results, with 23.8% of patients having near-normal HRSD scores and 58.8% of patients having more than 50% score reduction. In contrast, the results of the subgroup analysis showed that patient age, different tumor stages, and whether or not chemotherapy was synchronized had little effect on patients' depressive status scores before and after treatment. It suggests that the occurrence of TRDD is more related to the diagnosed tumor itself.

A randomized, placebo-controlled study reported by Yang Qing showed that fluvoxamine significantly attenuated depressive disorder and anxiety of cancer patients with MDD, with a 49.3% reduction in HAMD-17 scores and 54.7% reduction in HAMA scores[23]. In our study, after the treatment with fluvoxamine for 8 weeks, the reduction rate on HAMD-17 scores was 53.0% and the reduction rate on HAMA scores was 52.6% (Table 4 and 5), Which seemed to be greater in reduction rate on HAMD-17 scores (53% vs 49.3%) and slightly lower in reduction rate on HAMA scores (52.6% vs 54.7%), comparable to previous studies. Above all, the results mentioned above and the response rates and remission rates of MDD and anxiety make the results more valuable clinically.

A randomized, placebo-controlled study reported by Xiao Di showed that after 6 weeks of

fluvoxamine treatment on anxiety disorders, the response (the reduction rate of HAMA scores ≥ 50%) rate was 38.9%[24], which was slightly lower than the response rate of 50% in our study. A possible reason is that the treatment duration in the study by Xiao Di was shorter than that in ours, and therefore poor treatment limited the efficacy of the drug. When anxiety is not completely treated, a continuation of full-dose medication can increase the response rate. A randomized, placebo-controlled study reported by Lv YL showed that after 8 weeks of treatment with fluvoxamine, anxiety symptoms alleviated significantly, and the reduction of HAMA scores was 69.7%[25, 26], which was slightly higher than that in our study (52.6%). The reduction rate of anxiety in cancer patients with depressive disorder treated with fluvoxamine was 54.7% reported by Yang Q[23], which was comparable to the results in our study.

It was reported that fluvoxamine could increase serum melatonin and improve sleep quality[24]. After the treatment with fluvoxamine for 4 weeks, the serum melatonin concentration in cancer patients with the MDD was 52.89±7.35 ng/L, which was higher than patients treated with fluvoxamine of 40.46±3.76 ng/L[23]. In our study, the increasing rate of total MOS-SS scores was 53.7%. It seemed that fluvoxamine significantly improved the sleep quality of cancer patients treated due to increased serum melatonin.

Many studies demonstrated that fluvoxamine was safe and well-tolerated[19, 26]. The study by Gothelf D showed that 100 mg of fluvoxamine daily for cancer children and adolescents with MDD, and anxiety was safe and well-tolerated, with only 2 patients (13.3%) showing stomachache and 1 patient (6.7%) with dry mouth, nausea, and diarrhea[27]. Gothelf's study indicated that fluvoxamine was well-tolerated among children and adolescents with cancer. As the sample size was small (15 cases), further research and validation were needed. No adverse events occurred when gynecological cancer patients with MDD were treated with fluvoxamine for 8 weeks, as reported by Suzuki N.[28]. Hayashi K found that fluvoxamine could inhibit glioblastoma multiforme cell migration and invasion without drug toxicity[29]. In addition, an observational study with large samples conducted in Taiwan showed that SSRIs such as fluvoxamine could reduce liver cancer risk[30].

Our study found that fluvoxamine could alleviate MDD and anxiety and improve the sleep quality of cancer patients with moderate to severe MDD. However, there are still limitations to this study. This study was a single-arm study rather than a randomized, double-blind clinical trial. Although the study was conducted in 7 centers nationwide, the total number of samples included was only 101. Therefore, the sample size may not be enough to analyze whether the results were consistent among different cancer types and treatment methods. There are reasons for the design that choose single-arm trial. First, the effect of individual differences can be avoided; then, using a placebo for moderately to severely depressed subjects is contrary to the principles of depression treatment guidelines and against medical ethics. The overall dropout rate in this study was 20.8%, including 13 (12.9%) patients who failed to finish the follow-up and 8 (7.9%) patients who could not tolerate the adverse reactions of anticancer treatment or died. The lack of a placebo-controlled group made it impossible to achieve a definite conclusion about the efficacy of fluvoxamine on cancer patients with moderate to severe depressive disorder. In addition, this study focused on treating MDD, anxiety, and sleep disorder, but did not monitor the changes in life quality and the overall survival rate of cancer patients after antidepressant treatment. These factors referred to above should be further investigated in future research.

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Conflict of Interests

The authors declare no Conflict of Interest.

References Références Referencias

1. Mitchell AJ, Chan M, Bhatti H, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies[J]. The Lancet Oncology, 2011, 12(2): 160-74.
2. Choo CC, Chew PKH, Lai SM, et al. Effect of Cardiac Rehabilitation on Quality of Life, Depression and Anxiety in Asian Patients[J]. International journal of environmental research and public health, 2018, 15(6).
3. Arrieta O, Angulo LP, Núñez-Valencia C, et al. Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer[J]. Annals of surgical oncology, 2013, 20(6): 1941-8.
4. Colleoni M, Mandala M, Peruzzotti G, et al. Depression and degree of acceptance of adjuvant cytotoxic drugs[J]. Lancet, 2000, 356(9238):1326-7.

5. Prieto JM, Blanch J, Atala J, et al. Psychiatric morbidity and impact on hospital length of stay among hematologic cancer patients receiving stem-cell transplantation[J]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 2002, 20(7): 1907-17.
6. Kim Y, Spillers RL. Quality of life of family caregivers at 2 years after a relative's cancer diagnosis[J]. Psycho-oncology, 2010, 19(4): 431-40.
7. Pinquart M, Duberstein PR. Depression and cancer mortality: a meta-analysis[J]. Psychological medicine, 2010, 40(11): 1797-810.
8. Lloyd-Williams M, Shiels C, Taylor F, et al. Depression--an independent predictor of early death in patients with advanced cancer[J]. Journal of affective disorders, 2009, 113(1-2): 127-32.
9. Satin JR, Linden W, Phillips MJ. Depression as a predictor of disease progression and mortality in cancer patients: a meta-analysis[J]. Cancer, 2009, 115(22):5349-61.
10. Riba MB, Donovan KA, Andersen B, et al. Distress Management, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology[J]. Journal of the National Comprehensive Cancer Network: JNCCN, 2019, 17(10):1229-49.
11. Ng CG, Boks MP, Zainal NZ, et al. The prevalence and pharmacotherapy of depression in cancer patients[J]. Journal of affective disorders, 2011, 131(1-3): 1-7.
12. Rayner L, Price A, Evans A, et al. Antidepressants for depression in physically ill people[J]. The Cochrane database of systematic reviews, 2010, (3):Cd007503.
13. Rayner L, Price A, Evans A, et al. Antidepressants for the treatment of depression in palliative care: systematic review and meta-analysis[J]. Palliative medicine, 2011, 25(1):36-51.
14. Fisch MJ, Loehrer PJ, Kristeller J, et al. Fluoxetine versus placebo in advanced cancer outpatients: a double-blinded trial of the Hoosier Oncology Group[J]. Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 2003, 21(10): 1937-43.
15. Holland JC, Romano SJ, Heiligenstein JH, et al. A controlled trial of fluoxetine and desipramine in depressed women with advanced cancer[J]. Psycho-oncology, 1998, 7(4): 291-300.
16. Holland JC, Jacobsen PB, Riba MB. NCCN: Distress management[J]. Cancer control: journal of the Moffitt Cancer Center, 2001, 8(6 Suppl 2):88-93.
17. Hindmarch I, Hashimoto K. Cognition and depression: the effects of fluvoxamine, a sigma-1 receptor agonist, reconsidered[J]. Human psychopharmacology, 2010, 25(3): 193-200.
18. March JS, Kobak KA, Jefferson JW, et al. A double-blind, placebo-controlled trial of fluvoxamine versus imipramine in outpatients with major depression[J]. The Journal of clinical psychiatry, 1990, 51(5):200-2.
19. Omori IM, Watanabe N, Nakagawa A, et al. Efficacy, tolerability and side-effect profile of fluvoxamine for major depression: meta-analysis[J]. Journal of psychopharmacology (Oxford, England), 2009, 23(5): 539-50.
20. Hamilton M. A rating scale for depression[J]. Journal of neurology, neurosurgery, and psychiatry, 1960, 23(1): 56-62.
21. Zanardi R, Franchini L, Serretti A, et al. Venlafaxine versus fluvoxamine in the treatment of delusional depression: a pilot double-blind controlled study[J]. The Journal of clinical psychiatry, 2000, 61(1): 26-9.
22. Clerc G. Antidepressant efficacy and tolerability of milnacipran, a dual serotonin and noradrenaline reuptake inhibitor: a comparison with fluvoxamine[J]. International clinical psychopharmacology, 2001, 16(3): 145-51.
23. Yang Q, Shaofeng Y, Lulu Zhang, et al. Effects of fluphenazine on serum melatonin of patients with post-cancer depression[J]. Chinese journal of clinical healthcare, 2017, 20(6): 676-8.[in Chinese]
24. Di X,Xiaojuan L, Yanfeng Z, et al. Clinical study of fluvoxamine combined with cognitive therapy for chronic anxiety disorder[J]. Journal of Clinal Medicine, 2019, 6(8):38-9,41.[in Chinese]
25. Yongliang L, Hongliang Z, Lijie C. et al. Fluvoxamine in treating depressive disorder with anxiety [J]. Journal of Clinical Psychiatry, 2010, 20(6):406-7.[in Chinese]
26. Westenberg HG, Sandner C. Tolerability and safety of fluvoxamine and other antidepressants[J]. International journal of clinical practice, 2006, 60(4): 482-91.
27. Gothelf D, Rubinstein M, Shemesh E, et al. Pilot study: fluvoxamine treatment for depression and anxiety disorders in children and adolescents with cancer[J]. Journal of the American Academy of Child and Adolescent Psychiatry, 2005, 44(12): 1258-62.
28. Suzuki N, Ninomiya M, Maruta T, et al. Clinical study on the efficacy of fluvoxamine for psychological distress in gynecologic cancer patients[J]. International journal of gynecological cancer: official journal of the International Gynecological Cancer Society, 2011, 21(6):1143-9.
29. Hayashi K, Michiue H, Yamada H, et al. Fluvoxamine, an anti-depressant, inhibits human glioblastoma invasion by disrupting actin polymerization[J]. Scientific reports, 2016, 6: 23372.
30. Chan HL, Chiu WC, Chen VC, et al. SSRIs associated with decreased risk of hepatocellular carcinoma: A population-based case-control study[J]. Psycho-oncology, 2018, 27(1): 187-92.