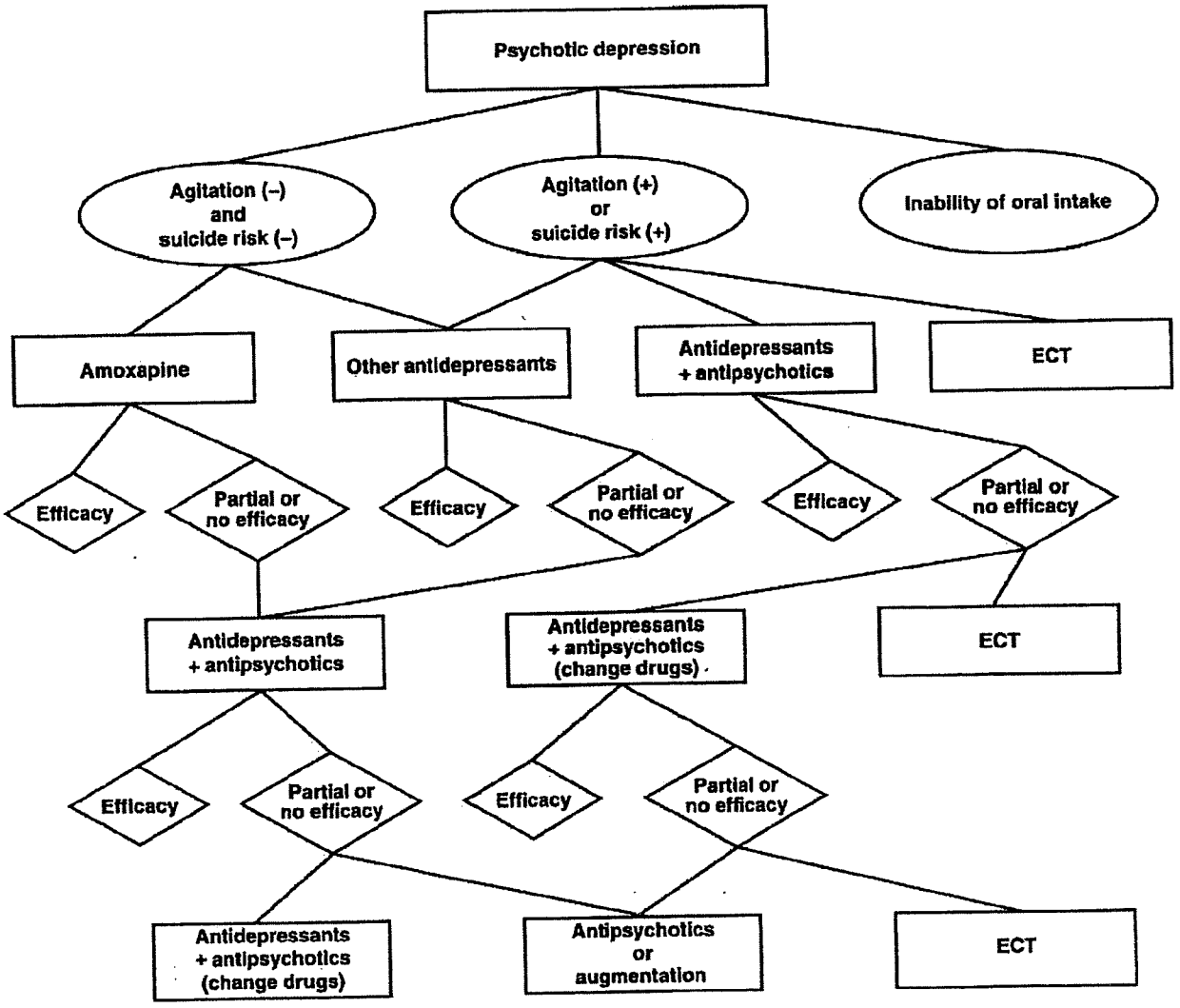


Figure 3. Algorithm for the treatment of psychotic depression.

antidepressants such as amoxapine or fluvoxamine is recommended as one of the first choices [23–25] (level B). For the treatment of psychotic depression with a high risk of suicide or agitation, an antidepressant-antipsychotic combination [23,24,26] or ECT [27] (level A) is recommended. Combination therapy with SSRIs and atypical antipsychotics may be helpful [28] (level B). In the case of partial or no efficacy, augmentation, switching to another combination of antidepressant and antipsychotic, or ECT can be chosen as the second- and third-line treatments.

Algorithm for the treatment of bipolar disorder, manic episode (Figure 4)

The diagnosis of mania is according to the DSM-IV criteria. The first-line treatment is mood stabilizers. There is no difference in antimanic efficacy among lithium, carbamazepine, and valproate [29–31] (level A). Valproate seems to be favorable in the treatment of mixed mania [31] (level B). Antipsychotics such as sultopride [32] (level B) and zotepine [33] (level B), alone or in combination with mood stabilizers, are often used for the treatment of mania. Recently, atypical antipsychotics, olanzapine [34] (level A), quetiapine [35] (level A), and risperidone [36–38] (level A) are preferred because of their low incidence of extrapyramidal side effects. A combination of mood stabilizers may be helpful [39] (level B). Furthermore, ECT could be chosen when pharmacotherapy fails [40] (level A).

Algorithm for the treatment of bipolar disorder, depressive episode (Figure 5)

Patients with bipolar disorder sometimes become depressed even under treatment with lithium. However, there are a limited number of studies available in these cases. An increase in the dose of lithium, the use of carbamazepine or valproate, or the addition of antidepressants such as SSRI or SNRI can be selected [41–43] (level B). ECT is an option for the treatment of refractory bipolar depression.

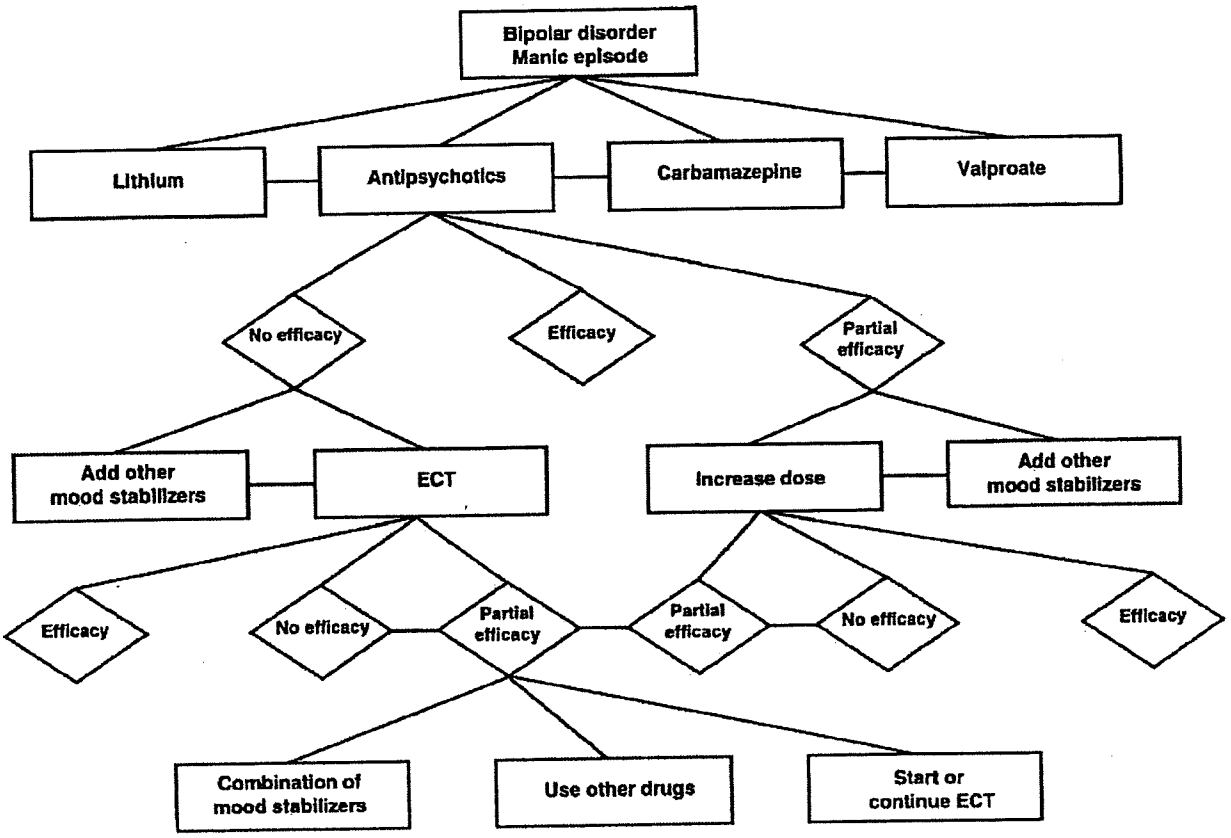


Figure 4. Algorithm for the treatment of bipolar disorder, manic episode.

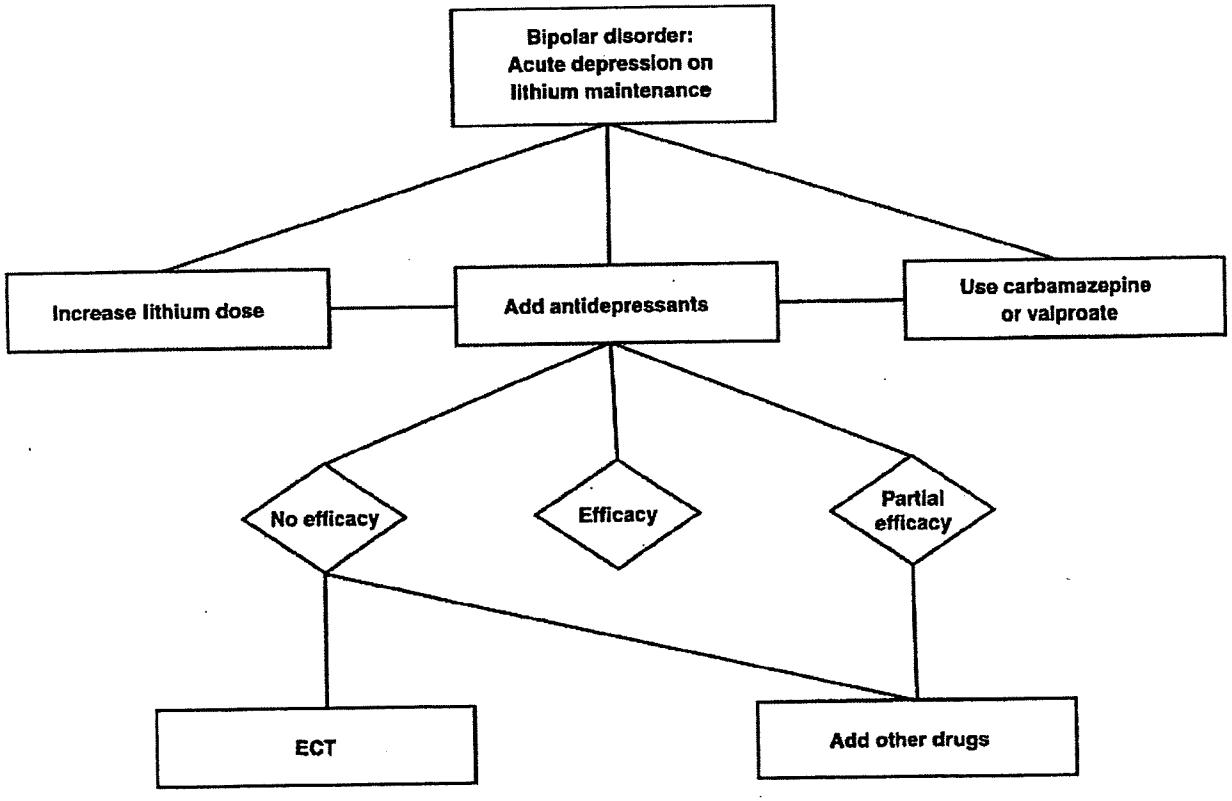


Figure 5. Algorithm for the treatment of bipolar disorder, depressive episode.

Algorithm for the treatment of rapid cycling mood disorder (Figure 6)

The diagnosis of rapid cycling (RC) is according to the DSM-IV criteria. RC is sometimes induced by hypothyroidism, female hormone disturbance, organic brain syndrome, or antidepressant treatment. Most clinical studies on RC are based primarily on group consensus, with minimal research-based evidence but significant clinical experience (level C). The first-line treatment is valproate or carbamazepine [44,45]. Because carbamazepine might induce severe side effects, valproate may be preferable. Although RC is usually resistant to lithium, the combination of lithium and valproate (or carbamazepine) may be helpful in cases of partial or no efficacy. Another option is to add levothyroxine to mood stabilizers [46]. Where the above treatment does not show any efficacy, clonazepam [47], atypical antipsychotics such as olanzapine [48], or ECT [49] can be used.

Discussion

We have demonstrated the revised Japanese version of the algorithms for the treatment of mood disorders. As compared to the first version of the algorithms [2], major differences are the availability of newer antidepressants (fluvoxamine, paroxetine, and milnacipran) and antipsychotics (quetiapine and olanzapine). Moreover, an anticonvulsant, valproate, was approved for the treatment of bipolar disorder in 2002.

As for major depressive disorder, mild or moderate, the first-line treatment is SSRIs or SNRIs instead of TCAs, nonTCAs, or sulpiride. With regard to sulpiride, its clinical efficacy is not definite [50] (level B) and it is sometimes associated with side effects such as hyperprolactinemia, weight gain, and extrapyramidal signs. Thus, we do not recommend it as the first-line treatment in this version.

While lithium, carbamazepine, and antipsychotics such as zotepine and sultopride were recommended

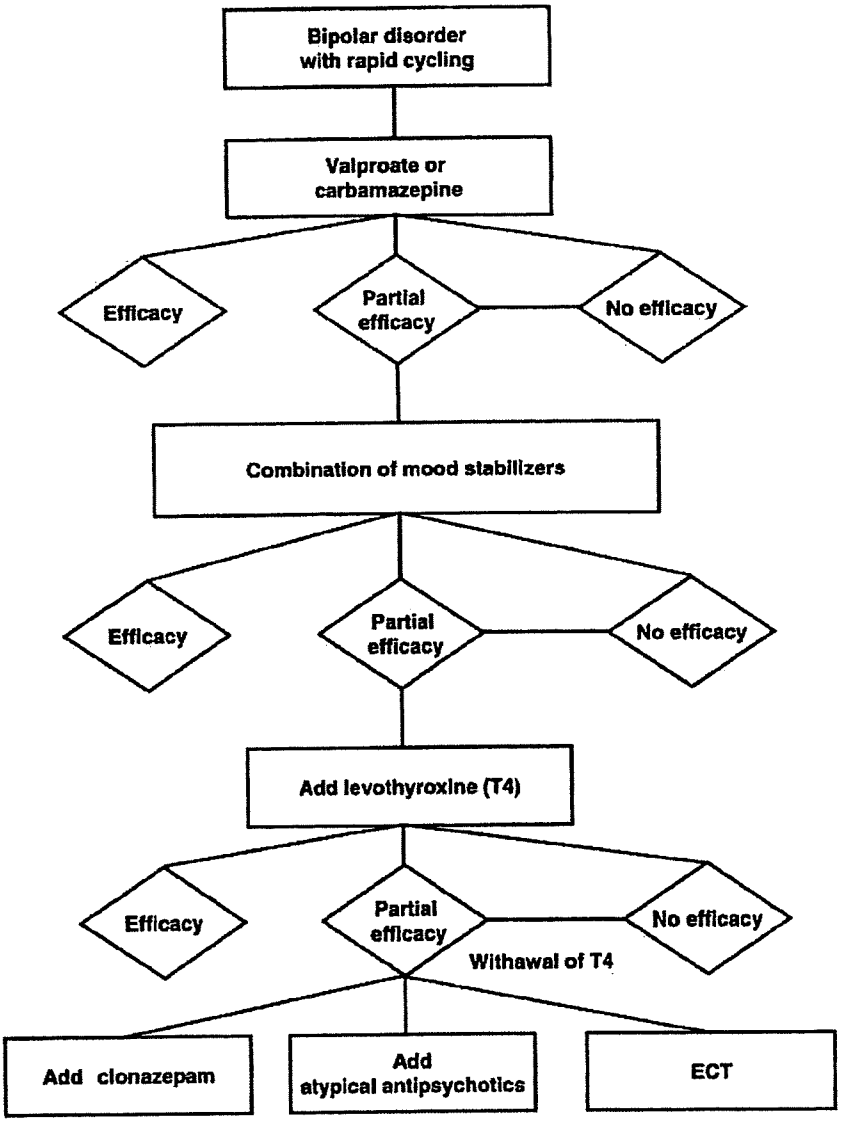


Figure 6. Algorithm for the treatment of rapid cycling mood disorder.

for the initial treatment of mania in the first version, valproate and novel antipsychotics such as quetiapine and olanzapine can be chosen in this revised version. Furthermore, valproate is also preferred for the first-line treatment of rapid cycling mood disorders because of its safety.

As for severe non-psychotic depression, psychotic depression, and bipolar depression, the revised treatment algorithms are similar to the original ones.

Except for clinical trials to approve new drugs, only a few RCTs have been conducted in Japan. Thus, most of the studies useful for the development of these revised algorithms were not conducted in Japan. Because clinical psychopharmacological evidence is insufficient, more and more randomized, placebo-controlled studies should be conducted to accumulate good research-based evidence in Japan. Furthermore, we have just begun to evaluate clinical outcomes following the use of these algorithms.

Key points

- Revised psychopharmacology algorithms for the treatment of mood disorders have been presented
- These algorithms have been developed according to methods based on clinical psychopharmacological evidence, the results of a questionnaire survey sent to 200 Japanese psychiatrists, and the consensus of all the research members
- The algorithms consist of six categories including major depression and bipolar disorder
- Clinical psychopharmacological evidence is insufficient in Japan

Statement of interest

The authors have no conflict of interest with any commercial or other associations in connection with the submitted article.

Acknowledgement

A part of this work was supported by a grant from the Ministry of Health, Welfare, and Labour in Japan.

References

[1] Murray CLJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997;349:1436–42.

[2] Higuchi T, Fujiwara Y, Iida M, et al. Algorithm for the treatment of mood disorders in Japan. Int J Psychiatr Clin Pract 1999;3:277–85.

[3] Sato M, Nakane N, Hayashida M, T, et al. Algorithms for the treatment of schizophrenia in Japan. Int J Psychiatr Clin Pract 1999;3:271–6.

[4] Shioe K. Pharmacotherapy of depression. Clinical Psychiatry 2006;46:1335–45 (in Japanese).

[5] Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. J Affect Disrord 2000;58:19–36.

[6] Montgomery SA. A meta-analysis of the efficacy and tolerability of paroxetine versus tricyclic antidepressants in the treatment of major depression. Int Clin Psychopharmacol 2001;16:169–78.

[7] Aoba A, Tanaka Y, Kageyama S, et al. A post-marketing clinical study of paroxetine hydrochloride hydrate in patients with depression or depressive episodes: A double-blind, imipramine hydrochloride-controlled, comparative study. Jpn J Clin Psychopharmacol 2004;7:831–53 (in Japanese).

[8] Asakura M, Tajima O. A randomized, double-bind study of fluvoxamine maleate inpatients with depression or depressive state: A comparison in anticholinergic effects and cardiovascular adverse reactions between fluvoxamine malcate and imipramine hydrochloride. Jpn Pharmacol Ter 2005;33:773–87.

[9] Otsubo T, Akimoto Y, Yamada H, et al. A comparative study of the efficacy and safety profiles between fluvoxamine and nortriptyline in Japanese patients with major depression. Pharmacopsychiatry 2005;38:30–5.

[10] Puech A, Montgomery SA, Prost JF, Solles A, Briley M. Milnacipran, a new serotonin and noradrenaline reuptake inhibitor: an overview of its antidepressant activity and clinical tolerability. Int Clin Psychopharmacol 1997;12:99–108.

[11] Furukawa TA, Streiner DL, Young LT. Antidepressant and benzodiazepine for major depression. Cochrane Database Syst Rev 2002;1:CD001026.

[12] Kennedy S, McIntyre R, Fallu A, Lam R. Pharmacotherapy to sustain the fully remitted state. J Psychiatry Neurosci 2002;27:269–80.

[13] Baker CB, Tweedie R, Duval S, Woods SW. Evidence that the SSRI dose response in treating major depression should be reassessed: a meta-analysis. Depress Anxiety 2003;17: 1–9.

[14] Bauer M, Forsthoff A, Baethge C, et al. Lithium augmentation therapy in refractory depression – Update 2002. Eur Arch Psychiatry Clin Neurosci 2003;253:132–9.

[15] Aronson R, Offman HJ, Joffe RT, Naylor CD. Triiodothyronine augmentation in the treatment of refractory depression. A meta-analysis. Arch Gen Psychiatry 1996;53:842–8.

[16] Shelton RC, Tollefson GD, Tohen M, et al. A novel augmentation strategy for treating resistant major depression. Am J Psychiatry 2001;158:131–4.

[17] Inoue T, Tsuchiya K, Miura J, et al. Bromocriptine treatment of tricyclic and heterocyclic antidepressant-resistant depression. Biol Psychiatry 1996;40:151–3.

[18] Segrave R, Nathan PJ. Pindolol augmentation of selective serotonin reuptake inhibitors: Accounting for the variability of results of placebo-controlled double-blind studies in patients with major depression. Hum Psychopharmacol 2005;20:163–74.

[19] Landen M, Bjorling G, Agren H, Fahlen T. A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. J Clin Psychiatry 1998;59:664–8.

[20] Appelberg BG, Syvalahti EK, Koskinen TE, Mehtonen OP, Muhonen TT, Naukkarinen HH. Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in study. J Clin Psychiatry 2001;62:448–52.

[21] The UK ECT review group. Efficacy and safety of electroconvulsive therapy in depressive disorder: a systematic review and meta-analysis. Lancet 2003;361:799–808.

[22] Tzanakaki M, Guazzelli M, Nimatoudis I, Zissis NP, Smeraldi E, Rizzo F. Increased remission rates with venlafaxine compared with fluoxetine in hospitalized patients with major depression and melancholia. Int Clin Psychopharmacol 2000;15:29–34.

[23] Anton RF Jr, Burch EA Jr. Amoxapine versus amitriptyline combined with perphenazine in the treatment of psychotic depression. Am J Psychiatry 1990;147:1203–8.

[24] Anton RF Jr, Burch EA Jr. Response of psychotic depression subtypes to pharmacotherapy. J Affect Disord 1993;28: 125–31.

[25] Zanardi R, Franchini L, Serretti A, Perez J, Smeraldi E. Venlafaxine versus fluvoxamine in the treatment of delusional depression: a pilot double-blind controlled study. J Clin Psychiatry 2000;61:26–9.

[26] Spiker DG, Weiss JC, Delay RS, et al. The pharmacological treatment of delusional depression. Am J Psychiatry 1985; 142:430–6.

[27] Kho KH, van Vreeswijk MF, Simpson S, Zwinderman AH. A meta-analysis of electroconvulsive therapy efficacy in depression. J ECT 2003;19:139–47.

[28] Rothschild AJ, Williamson DJ, Tohen MF, et al. A double-blind, randomized study of olanzapine and olanzapine/fluoxetine combination for major depression with psychotic features. J Clin Psychopharmacol 2004;24:365–73.

[29] Emilien G, Maloteaux JM, Seghers A, Charles G. Lithium compared to valproic acid and carbamazepine in the treatment of mania. A statistical meta-analysis. Eur Neuropsychopharmacol 1996;6:245–52.

[30] Poolsup N, Li Wan Po A, de Oliveira IR. Systematic overview of lithium treatment in acute mania. J Clin Pharm Ther 2000;25:139–56.

[31] Macritchie K, Geddes JR, Scott J, Haslam D, de Lima M, Goodwin G. Valproate for acute mood episodes in bipolar disorder. Cochrane Database Syst Rev 2003;1:CD004052.

[32] Kudo Y, Ichimaru S, Kawakita Y, et al. Comparison of therapeutic effect on mania of sultopride hydrochloride with haloperidol using double-blind technique. Clin Eval 1987;15:15–36 (in Japanese).

[33] Harada T, Otsuki S, Yamashita I, et al. Double-blind comparative study on antimanic effects of zotepine and lithium carbonate. Jpn J Clin Psychiatry 1994;23:1249–62 (in Japanese).

[34] Rendell JM, Gijsman HJ, Keck P, Goodwin GM, Geddes JR. Olanzapine alone or in combination for acute mania. Cochrane Database Syst Rev 2003;3:CD004040.

[35] Vieta E, Mullen J, Brecher M, Paulsson B, Jones M. Quetiapine monotherapy for mania associated with bipolar disorder: combined analysis of two international, double-blind, randomised, placebo-controlled studies. Curr Med Res Opin 2005;21:923–34.

[36] Segal J, Berk M, Brook S. Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial. Clin Neuropharmacol 1998;21: 176–80.

[37] Yatham LN, Grossman F, Augustynus I, Vieta E, Ravindran A. Mood stabilisers plus risperidone or placebo in the treatment of acute mania: International, double-blind, randomised controlled trial. Br J Psychiatry 2003;182: 141–7.

[38] Hirschfeld RMA, Keck PE Jr, Kramer M, et al. Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial. Am J Psychiatry 2004;161:1057–65.

[39] Small JG, Klapper MH, Marhenke JD, Milstein V, Woodham GC, Kellams JJ. Lithium combined with carbamazepine or haloperidol in the treatment of mania. Psychopharmacol Bull 1995;31:265–72.

[40] Mukherjee S, Sackeim HA, Schnur DB. Electroconvulsive therapy of acute manic episodes: a review of 50 years' experience. Am J Psychiatry 1994;151:169–76.

[41] Nemeroff CB, Evans DL, Guylai L, et al. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. Am J Psychiatry 2001;158:906–12.

[42] Young LT, Joffe RT, Robb JC, MacQueen GM, Marriott M, Patelis-Siotis I. Double-blind comparison of addition of a second mood stabilizer versus an antidepressant to an initial mood stabilizer for treatment of patients with bipolar depression. Am J Psychiatry 2000;157:124–6.

[43] Vieta E, Martinez-Aran A, Goikolea JM, et al. A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers. J Clin Psychiatry 2002;63:508–12.

[44] Calabrese JR, Delucchi GA. Spectrum of efficacy of valproate in 55 patients with rapid-cycling bipolar disorder. Am J Psychiatry 1990;147:431–4.

[45] Joyce PR. Carbamazepine in rapid cycling bipolar affective disorder. Int Clin Psychopharmacol 1988;3:123–9.

[46] Bauer MS, Whybrow PC. Rapid cycling bipolar affective disorders. II. Treatment of refractory rapid cycling with high-dose levothyroxine. Arch Gen Psychiatry 1990;47:435–40.

[47] Morishita S, Aoki S, Watanabe S. Clonazepam as a therapeutic adjunct to improve the management of psychiatric disorders. Psychiatry Clin Neurosci 1998;52:75–8.

[48] Sanger TM, Tohen M, Vieta E, et al. Olanzapine in the acute treatment of bipolar I disorder with a history of rapid cycling. J Affect Disord 2003;73:155–61.

[49] Wehr TA, Sack DA, Rosenthal NE, Cowdry RW. Rapid cycling affective disorder: contributing factors and treatment responses in 51 patients. Am J Psychiatry 1988;145:179–84.

[50] Standish-Barry HM, Bouras N, Bridges PK, Watson JP. A randomized double blind group comparative study of sulpiride and amitriptyline in affective disorder. Psychopharmacology 1983;81:258–60.

Psycho-Oncology
Psycho-Oncology **17**: 466–473 (2008)
Published online 7 September 2007 in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/pon.1259

Negative psychological aspects and survival in lung cancer patients

Naoki Nakaya[1,2], Kumi Saito-Nakaya[1], Tatsuo Akechi[3], Shinichi Kuriyama[2], Masatoshi Inagaki[1], Nobutaka Kikuchi[2], Kanji Nagai[4], Shoichiro Tsugane[5], Yutaka Nishiwaki[4], Ichiro Tsuji[2] and Yosuke Uchitomi[1]*

[1]*Psycho-Oncology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Japan*
[2]*Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan*
[3]*Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan*
[4]*Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan*
[5]*Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan*

**Correspondence to: Psycho-Oncology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa 277-8577, Japan. E-mail: yuchitom@east.ncc.go.jp*

Received: 7 February 2007
Revised: 25 June 2007
Accepted: 7 July 2007

Abstract

We conducted a prospective cohort study in Japan to investigate associations between negative psychological aspects and cancer survival. Between July 1999 and July 2004, a total of 1178 lung cancer patients were enrolled. The questionnaire asked about socioeconomic variables, smoking status, clinical symptoms, and psychological aspects after diagnosis. Negative psychological aspects were assessed for the subscales of helplessness/hopelessness and depression. Clinical stage, performance status (PS), and histologic type were obtained from medical charts. The subjects were followed up until December 2004, and 686 had died. A Cox regression model was used to estimate the hazards ratio (HR) of all-cause mortality. After adjustment for socioeconomic variables and smoking status in addition to sex, age, and histologic type, both helplessness/hopelessness and depression subscales showed significant linear positive associations with the risk of mortality (p for trend < 0.001 for both). However, after adjustment for clinical state variables in addition to sex, age, and histologic type, these significant linear positive associations were no longer observed (p for trend $= 0.41$ and 0.26, respectively). Our data supported the hypothesis that the association between helplessness/hopelessness and depression and the risk of mortality among lung cancer patients was largely confounded by clinical state variables including clinical stage, PS, and clinical symptoms.

Keywords: cancer survival; depression; helplessness/hopelessness; neuroticism; prospective cohort study

Introduction

Negative psychological aspects, including depression, are common among cancer patients [1]. It has been reported that between 8% [2] and 44% [3] of lung cancer patients suffer from depression [2–7]. Furthermore, it has been suggested that negative psychological aspects affect the prognosis [8–14] as well as the quality of life of lung cancer patients [6,15,16].

In a recent review of studies that investigated the associations between the psychological aspects and the risk of mortality in cancer patients [17], it was revealed that helplessness/hopelessness [8,9] and depression [11,14] affected the mortality risk in cancer patients. It has been hypothesized that negative psychological aspects might affect the risk of mortality in cancer patients via endocrinological and/or immunological pathways [18,19] or poor compliance with cancer treatment [20].

Another possible interpretation of the increased mortality observed in cancer patients with negative psychological aspects is that the negative psychological aspects may simply reflect a poor clinical state, which by itself would be associated with an increased mortality in cancer patients. Depression has been reported to be strongly associated with poor clinical state such as the tumor stage, performance status (PS), and severity of clinical symptoms [7,21]. In addition, the severity of clinical symptoms, such as pain and dyspnea, was shown to be an important independent prognostic factor in a population with lung cancer patients [22,23]. The clinical state indices are thus important confounders that must be taken into account in the evaluation of the association between negative psychological aspects and the risk of mortality among cancer patients. Most previous studies suggesting the existence of the above association had a limitation in that they failed to sufficiently control for the effect of the clinical state of the patients [10–16].

The purpose of this study was to test the hypothesis that the association between the nega-

tive psychological aspects and the risk of mortality among lung cancer patients is confounded by the poor clinical state of the patients. If this hypothesis were proved, it would reassure cancer patients because poor psychological states in cancer patients may merely be a consequence of illness but not a determinant of poor prognosis. In order to test the hypothesis, we conducted a prospective cohort study using the Lung Cancer Database Project (LCDP) at the National Cancer Center Hospital East (NCCHE), Japan. This study has enrolled the largest number of subjects ($N = 1178$), recorded the largest number of deaths ($N = 686$), and had the longest follow-up periods (29 063 person-months) of all studies to date and also extensively controlled for possible confounders, including the clinical states, socioeconomic variables, and the smoking status.

Methods

Study participants

The study design has been reported in detail elsewhere [24]. Briefly, these data were derived from the LCDP at the NCCHE, Japan. The inclusion criteria of the patients were newly diagnosed as lung cancer from July 1999 through July 2004 at the NCCHE. We invited 2036 consecutive patients who participated in the LCDP. Of those, 1995 patients gave their consent. Three psychological questionnaires, namely, the Eysenck Personality Questionnaire-Revised (EPQ-R) [25], the Mental Adjustment to Cancer Scale (MACS) [26], and the Hospital Anxiety and Depression Scale (HADS) [27] were distributed to the subjects. Because we had discontinued the above psychological questionnaire surveys in August 2003 for non-academic reasons, 414 patients who entered the LCDP after August 2003 were ineligible for the present study. Consequently, 1581 patients were included for the analysis in this study. We excluded patients with: (1) concomitant cancer ($n = 39$), (2) duplicate cancer ($n = 149$), and (3) responses missing for any of the items related to the subscales of this study (neuroticism, helplessness/hopelessness, and depression) ($n = 215$). Finally, we analyzed 1178 patients with lung cancer for this study. The patients completed the questionnaires by themselves at home before admission.

The characteristics of the patients who were included in this study (1178 patients) or excluded (403 patients) from this study were similar (mean age at diagnosis in years, 64 vs 66; women, 29 vs 28%; clinical stage, IA–IIB 44 vs 45%, IIIA–IIIB 30 vs 25%, and IV 27 vs 28%; PS, PS0 41 vs 47%, and PS$\geqslant$1 59 vs 53%, respectively).

The questionnaire also included questions pertaining to socioeconomic variables, smoking status, clinical state, and the psychological aspects of the patients.

Medical information about the patients was obtained from the patients' medical charts. A trained research nurse (KS-N) who was blinded to the outcome of the individual patients conducted a chart review to extract the histologic type, clinical stage, PS, and severity of self-reported pain and dyspnea.

All patients provided their written informed consent. The project was approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center, Japan (in March 1999).

Socioeconomic variables, smoking, and the clinical state

Information, including the age at diagnosis, sex, socioeconomic variables (educational level, marital status, and cohabitation), smoking status, and severity of clinical symptoms (self-reported pain and dyspnea), was obtained from the self-administered questionnaires.

Medical information, including the clinical stage, PS, or histologic type, was obtained from the patients' medical charts. The clinical stage of lung cancer was classified according to the TNM classification of the International Union Against Cancer. The PS was assessed by the attending physician of each patient using the Eastern Cooperative Oncology Group criteria [28]. Self-reported pain and dyspnea at the time of diagnosis were self-graded on a four-point scale: 1 (none), 2 (mild), 3 (moderate), 4 (severe), or 5 (very severe) [2].

Negative psychological aspects

Neuroticism

The personality trait of the neuroticism subscale was measured with the Japanese version of EPQ-R [25,29]. The subscale contains 12 questions with dichotomized responses (yes or no), with the total scores for the items ranging from 0 to 12. Higher scores indicate a greater tendency toward emotional instability.

Helplessness/hopelessness

The coping style of the helplessness/hopelessness subscale was measured with the Japanese version of MACS [26,30]. The subscale contains six questions, each question rated on a scale of 1 (definitely does not apply to me) to 4 (definitely applies to me). Higher scores indicate a greater tendency of the patients toward exhibiting a feeling of hopelessness and helplessness about themselves and their future because of having cancer, with a wholly pessimistic attitude.

Depression

Depressive symptoms were measured using the Japanese version of HADS [27,31]. The subscale contains seven questions, and each question is rated on a four-point scale of 0–3. Higher scores indicate greater depressive symptoms.

Follow-up

Survival until December 31, 2004, was confirmed by referring to the medical records, by mailing the patients, or from the annual residential registry, every year by members of our co-medical staff at the Division of Thoracic Oncology and the Psycho-Oncology Division. None of the subjects was lost to follow-up during the study period.

The person-months of follow-up were counted for each subject, from the date of the first visit to the NCCHE until the date of death or December 31, 2004, whichever occurred first. We accrued a total of 29 063 person-months and documented 686 deaths. However, we had no information on the cause of death.

Statistical analyses

The scores for each of the psychological subscales of neuroticism, helplessness/hopelessness, and depression were divided into four score levels approximately equal in size (quartiles) based on the scores of the subjects as a whole. Hazard ratios (HRs) were computed as the death rate among the subjects in each score level of the psychological subscale divided by the death rate among the subjects in the lowest score level. We used Cox proportional hazards regression to adjust for sex, age, and other potentially confounding variables [32] using the SAS PHREG program on the SAS statistical software package, version 9.1 (Cary, NC, USA). p Values for testing the statistical significance of the linear trends were calculated by treating the scores of each subscale as a continuous variable. p Values of less than 0.05 were considered to be statistically significant. All p Values were two-tailed.

We performed three multivariate analyses. Model 1 was adjusted for socioeconomic variables and smoking status as follows: educational level (high school or lower or higher) marital status (married, unmarried), cohabitation (living alone, living with someone), and smoking status (never smoker, ex-smoker, current smoker of 1–19 cigarettes per day, current smoker of 20 or more cigarettes per day) in addition to the age at diagnosis (continuous variable), sex, and histologic type (adenocarcinoma, squamous cell carcinoma, small cell carcinoma, large cell carcinoma, other). Model 2 was adjusted for clinical state variables as follows: clinical stage (IA–IIB, IIIA–IIIB, IV) and PS (0 or $1\leqslant$) in addition to the age at diagnosis, sex, and histologic type. Model 3 was adjusted for the clinical state variables, severity of self-reported pain, and dyspnea (none to mild or moderate to very severe) in addition to the factors adjusted for in model 2. For all models, the proportional hazard assumptions were tested and met.

Results

A total of 1178 lung cancer patients were enrolled in the study. The mean age of the patients was 64 years (SD 9) and 29% were women. Adenocarcinoma was the most common (58%), followed by squamous cell carcinoma (19%), small cell carcinoma (12%), large cell carcinoma (9%), and others (2%). As for the clinical stage, stage IA–IB was the most common (36%), followed by stage IIIA–IIIB (30%), stage IV (27%), and stage IIA–IIB (7%). As for PS, PS1 was the most common (53%), followed by PS0 (41%), PS2 (5%), and PS3 (1%).

Table 1 shows a comparison of the characteristics of the subjects between the highest and lowest score categories (divided into approximate quartiles) for each of the subscales of neuroticism, helplessness/hopelessness, and depression. Subjects with higher scores on the neuroticism subscale were more likely to be unmarried and to have a higher severity of pain and dyspnea. Subjects with higher scores on the helplessness/hopelessness subscale were more likely to be older and to have squamous cell carcinoma, more advanced cancer, poorer PS, and a higher severity of pain and dyspnea, and they were less likely to have a higher educational level. Subjects with higher scores on the depression subscale were more likely to have more advanced cancer, poorer PS, and a higher severity of pain and dyspnea.

After controlling for age at cancer diagnosis, sex and six variables, namely, histologic type (small cell or large cell carcinoma), smoking status (ex-smokers, currently smoking 1–19 cigarettes per day, or currently smoking 20 or more cigarettes per day), clinical stage (IIIA–IIIB or IV), PS ($1\leqslant$), self-reported pain (moderate to severe), and self-reported dyspnea (moderate to severe) were significantly positively associated with the risk of mortality among lung cancer patients as compared with that in each referent category (data not shown).

Neuroticism

For model 1, in which the estimated HR was adjusted for socioeconomic variables and the smoking status, we found no significant association between neuroticism and the risk of mortality in the lung cancer patients. The HR for the highest level of neuroticism vs hat for the lowest level was

Table I. Characteristics of the study subjects according to the highest and lowest of the neuroticism (EPQ-R), helplessness/hopelessness (MACS), and depression (HADS) subscales ($n = 1178$).

Score	Neuroticism (EPQ-R)		Helplessness/hopelessness (MACS)		Depression (HADS)	
	Q1 (lowest) ⩽3	Q4 (highest) 8⩽	Q1 (lowest) ⩽7	Q4 (highest) 14⩽	Q1 (lowest) ⩽2	Q4 (highest) 9⩽
Number of subjects	356	307	261	282	311	261
Mean (SD) age at the diagnosis	64 (9)	63 (10)	62 (10)	65 (9)	63 (6)	64 (9)
Women (%)	27	29	32	28	29	30
Histologic type (%)						
Adenocarcinoma	57	62	62	52	61	56
Squamous cell carcinoma	18	18	15	25	18	23
Small cell carcinoma	14	11	12	15	9	12
Large cell carcinoma	9	7	8	6	9	7
Other	2	3	3	2	2	2
Educational level (%)						
High school or less	78	76	70	85	73	78
College/University or higher	22	24	30	15	27	22
Marital status (%)						
Married	89	83	89	79	87	85
Unmarried	11	17	11	21	13	15
Cohabitation (%)						
Living alone	6	10	7	10	4	8
Living with another person	94	90	93	90	96	92
Smoking status (%)						
Never smokers	24	22	26	18	26	19
Ex-smokers	22	24	25	23	22	23
Current smokers						
1–19 cigarettes/day	11	10	9	13	11	11
20 or more cigarettes/day	43	43	40	45	41	46
Clinical stage[a] (%)						
IA–IIB	45	44	54	34	57	30
IIIA–IIIB	29	30	24	37	22	36
IV	25	26	22	29	21	34
Performance status[b] (%)						
0	45	39	47	31	56	26
1⩽	55	61	53	69	44	74
Self-reported pain (%)						
None to mild	90	86	91	81	93	78
Moderate to very severe	10	14	9	19	7	22
Self-reported dyspnea (%)						
None to mild	87	79	87	72	90	71
Moderate to very severe	12	21	13	28	10	29

[a] Clinical stages were defined by TNM classification: International Union Against Cancer.
[b] Performance status was defined by Eastern Cooperative Oncology Group (ECOG).

1.2 (95% confidence interval [95% CI], 0.9–1.4; p for trend = 0.13). We also conducted analyses by separately adjusting for the socioeconomic variables (p for trend = 0.10) and the smoking status (p for trend = 0.12) using this model, and the results remained unchanged. Moreover, even after adjustment for each clinical state variable (model 2 or model 3), we found no significant association between neuroticism and the risk of mortality (Table 2).

Helplessness/hopelessness

For model 1, in which the estimated HR was adjusted for socioeconomic variables and the smoking status, we found a significant, linear and positive association between helplessness/hopelessness and the risk of mortality. The HR for the highest level of helplessness/hopelessness vs that for the lowest level was 1.4 (95% CI, 1.1–1.8; p for trend < 0.001). We also conducted analyses by separately adjusting for the socioeconomic variables (p for trend < 0.001) and the smoking status (p for trend < 0.001) using this model, and the results remained unchanged. However, after adjustment for the clinical state variables (model 2 or model 3), the point estimate for the highest level was 1.1 or 1.0 as compared with that for the lowest level, and no significant association was observed (p for trend = 0.17 or 0.41, respectively) (Table 2).

Table 2. Hazard ratio (HR) for death from all causes among lung cancer patients according to the neuroticism (EPQ-R), helplessness/hopelessness (MACS), and depression (HADS) subscales ($n = 1178$)

	Q1 (lowest)	Q2	Q3	Q4 (highest)	p for trend
Neuroticism (EPQ-R)	⩽3	4–5	6–7	8⩽	
Number of deaths/total subjects	199/356	179/294	122/222	186/307	
Median survival in months (range)	24 (1–68)	21 (1–67)	24 (1–67)	22 (1–67)	
Multivariate model 1, HR (95% CI)	1.0 (referent)	1.1 (0.9–1.3)	1.1 (0.8–1.3)	1.2 (0.9–1.4)	0.13
Multivariate model 2, HR (95% CI)	1.0 (referent)	1.1 (0.9–1.3)	1.2 (0.9–1.5)	1.2 (1.0–1.5)	0.16
Multivariate model 3, HR (95% CI)	1.0 (referent)	1.1 (0.9–1.3)	1.1 (0.9–1.4)	1.2 (0.9–1.4)	0.48
Helplessness/hopelessness (MACS)	⩽7	8–10	11–13	14⩽	
Number of deaths/total subjects	137/261	196/349	165/286	188/282	
Median survival in months (range)	25 (1–68)	25 (1–67)	23 (1–67)	19 (1–67)	
Multivariate model 1, HR (95% CI)	1.0 (referent)	1.0 (0.8–1.3)	1.2 (0.9–1.5)	1.4 (1.1–1.8)	<0.001
Multivariate model 2, HR (95% CI)	1.0 (referent)	0.9 (0.7–1.1)	1.0 (0.8–1.2)	1.1 (0.9–1.4)	0.17
Multivariate model 3, HR (95% CI)	1.0 (referent)	0.9 (0.7–1.1)	0.9 (0.7–1.2)	1.0 (0.8–1.3)	0.41
Depression (HADS)	⩽2	3–5	6–8	9⩽	
Number of deaths/total subjects	151/311	190/330	165/276	180/261	
Median survival in months (range)	27 (1–68)	23 (1–67)	21 (1–67)	17 (1–67)	
Multivariate model 1, HR (95% CI)	1.0 (referent)	1.3 (1.0–1.6)	1.4 (1.1–1.7)	1.8 (1.5–2.3)	<0.001
Multivariate model 2, HR (95% CI)	1.0 (referent)	1.0 (0.8–1.2)	1.0 (0.8–1.3)	1.3 (1.0–1.6)	0.040
Multivariate model 3, HR (95% CI)	1.0 (referent)	1.0 (0.8–1.2)	1.0 (0.8–1.3)	1.2 (0.9–1.4)	0.26

Multivariate model 1 was adjusted for age at diagnosis, sex, histologic type, educational level (high school or lower or higher), marital status (married or unmarried), cohabitation (live alone or live with someone), and smoking (never smokers, ex-smokers, current smokers of 1–19 cigarettes per day, or current smokers of 20 or more cigarettes per day). Multivariate model 2 was adjusted for age at diagnosis, sex, histologic type, clinical stage (IA–IIB, IIIA–IIIB, or IV), and PS (0 or 1 ⩽). Multivariate model 3 was adjusted for the severity of self-reported pain and dyspnea (none to mild, moderate to very severe) in addition to the factors adjusted for in multivariate model 2. All hazard ratios (HRs) are given with 95% confidence intervals (CIs) in parentheses.

Depression

For model 1, in which the estimated HR was adjusted for socioeconomic variables and the smoking status, there was a significant, linear and positive association between depression and the risk of mortality. The HR for the highest level of depression vs that for the lowest was 1.8 (95% CI, 1.5–2.3; p for trend < 0.001). We also conducted analyses by separately adjusting for the socioeconomic variables (p for trend < 0.001) and the smoking status (p for trend < 0.001) using this model, and the results remained unchanged. After adjustment for the clinical state variables of clinical stage and PS (model 2), we still found significant linear positive association between depression and the risk of mortality (p for trend $= 0.040$). However, after adjustment for the clinical state variables of clinical stage, PS, and the self-reported pain and dyspnea (model 3), the point estimate for the highest level was 1.2 as compared with that for the lowest level, and no significant association was observed (p for trend $= 0.26$) (Table 2).

Association between clinical state variables and depression

We conducted a multivariate logistic regression analysis using a cross-sectional design to test the association between the clinical state variables and depression in the study patients (Table 3). Depression was defined based on a score of 9 or higher. The results indicated that more advanced clinical stage and a poorer PS were significantly associated with a higher prevalence of depression. The multivariate odds ratios (ORs) with reference to stage IA to IIB (95% confidence interval [CI]) were 1.6 (1.1–2.3) and 1.5 (1.0–2.3) in patients with stage IIIA–IIIB and IV, respectively. The multivariate OR with reference to PS0 (95% CI) was 1.8 (1.2–2.5) in patients with PS⩾1. Higher severity of pain and dyspnea was significantly associated with a higher prevalence of depression, independent of the clinical stage or PS. The multivariate OR with reference to none to mild self-reported pain (95% CI) was 1.6 (1.1–2.3) in patients with moderate to very severe self-reported pain. The multivariate OR with reference to none to mild self-reported dyspnea (95% CI) was 1.6 (1.1–2.3) in patients with moderate to very severe self-reported dyspnea.

Discussion

Earlier studies suggested that negative psychological aspects may increase the risk of mortality among cancer patients [8–14]. Our results clearly do not support the above hypothesis. We found that the association between negative psychological aspects and the mortality risk among lung cancer patients no longer remained significant after adjustments for the clinical state variables (clinical stage, PS, and self-reported pain and dyspnea). Our results endorsed the hypothesis that the associations were largely confounded by the clinical state variables.

Among the five prospective studies conducted to date [11–13,33,34], three reported a statistically

Table 3. Odds ratio (OR) from a multivariate logistic regression model for the clinical states and depression among lung cancer patients ($n = 1178$)

	Number of subjects	Number of depressed subjects (HADS score ⩾ 9)	OR (95% CI)	p Value (vs each referent category)
Clinical stage[a]				
IA–IIB	513	78	1.0 (referent)	—
IIIA–IIIB	348	93	1.6 (1.1–2.3)	0.021
IV	317	90	1.5 (1.0–2.3)	0.053
Performance status[b]				
0	487	68	1.0 (referent)	—
1 ⩽	691	193	1.8 (1.2–2.5)	0.003
Self-reported pain				
None to mild	1018	204	1.0 (referent)	—
Moderate to very severe	160	57	1.6 (1.1–2.3)	0.021
Self-reported dyspnea				
None to mild	957	185	1.0 (referent)	—
Moderate to very severe	220	76	1.6 (1.1–2.3)	0.007

This model was adjusted for age at diagnosis, sex, histologic type, clinical stage (IA–IIB, IIIA–IIIB, or IV), PS (0 or 1 ⩽), or the severity of self-reported pain and dyspnea (none to mild, moderate to very severe). All odds ratios (ORs) are given with 95% confidence intervals (CIs) in parentheses.

[a] Clinical stages were defined by TNM classification: International Union Against Cancer.

[b] Performance status was defined by Eastern Cooperative Oncology Group (ECOG).

significant positive association between depression and the risk of mortality among lung cancer patients [11–13]. Faller *et al.* [11] followed up 103 patients with stage I–IV lung cancer for 7–8 years and documented 92 deaths; they found a significant linear positive association between depression and the risk of mortality in the cancer patients (after inclusion of tumor stage, PS, and emotional distress level as covariates). Faller *et al.* [12] also followed up another series of 59 patients with advanced lung cancer (stage III or IV) for about 5 years and documented 54 deaths; they again reported a significant linear positive association between depression and the risk of mortality in the patients (after inclusion of age, sex, tumor stage, histologic type, and PS as covariates). Buccheri [13] followed up 133 patients with stage I–IV lung cancer for about 2 years and documented 44 deaths; subjects with higher scores for depressive symptoms exhibited a significantly higher risk of death as compared with subjects with lower scores (after inclusion of sex and tumor stage as covariates). All of these three studies had methodological limitations, that is, they included only a small number of subjects and failed to control sufficiently for potential confounding variables such as clinical symptoms, socioeconomic variables, and smoking status. In our study, adjustment for the effect of socioeconomic variables and smoking status (model 1) and for the effect of the clinical stage and PS as clinical state variables (model 2) did not alter the significant positive association between depression and mortality. However, when self-reported pain and dyspnea were included in the multivariate model (model 3), the association became non-significant (p for trend = 0.26) (Table 2). The severity of self-reported clinical symptoms, such as pain and dyspnea, was correlated with the tumor stage and/or PS among lung cancer patients [22,35]. However, the severity of self-reported pain and dyspnea was also described as an important independent prognostic factor in a population of lung cancer patients [22,23]. Therefore, when the association between the psychological state and cancer survival was examined, it was necessary to consider not only the tumor stage and the PS but also the severity of symptoms such as pain and dyspnea. Earlier studies were inadequate, even though the clinical stage and PS had been considered. As indicated in Table 3, the severities of self-reported pain and dyspnea were significantly associated with depression, independent of the clinical stage or PS. The severity of clinical symptoms reflected the severity of depressive symptoms among lung cancer patients. Thus, the association between depression and the risk of mortality was largely confounded by the clinical symptoms.

In the helplessness/hopelessness subscale, after adjustment for the effect of socioeconomic variables and smoking status (model 1), there was a significant, linear and positive association between helplessness/hopelessness and the risk of mortality. However, after inclusion of the clinical stage and PS (model 2) and the severity of self-reported pain and dyspnea in the multivariate model (model 3), the association became non-significant (p for trend = 0.17 and 0.41, respectively). For the association between the clinical state variables and the score in the helplessness/hopelessness subscale in the cross-sectional design, the results were similar to the results for depression (data not shown). Thus, the association between the score in the helplessness/hopelessness subscale and the risk of mortality was largely confounded by the clinical

state variables. On the other hand, no association was noted between the score for neuroticism and the risk of mortality, regardless of adjustment for any variables.

Our study had several methodological advantages as compared with previous studies. Firstly, our sample size was the largest (1178 eligible subjects and 686 deaths). Secondly, our study controlled extensively for potential confounding variables, including clinical state and socioeconomic variables and the smoking status.

However, our study also had several limitations. First, the study dealt with patients who were treated at one institution, a teaching cancer hospital in Japan; therefore, the external validity of the finding has to be tested. Second, we considered the negative psychological aspects in the patients before the start of treatment. The effect of the negative psychological aspects after the start of treatment upon the mortality should also have been tested. Third, the study subjects consisted entirely of lung cancer patients. Since patients with cancers at other sites were not examined in this study, it remains unclear whether the results can be extrapolated to patients with cancers at other sites. Fourth, we focused on the all-cause mortality, because we did not have information on the cause of death. Therefore, the association with the risk of death from lung cancer is unknown. Finally, because the follow-up period in this study was short and the number of patients with early-stage cancer was small, long-term follow-up of early-stage patients may also be warranted in the future.

In conclusion, negative psychological aspects such as neuroticism, helplessness/hopelessness, and depression were no longer associated with the risk of mortality among lung cancer patients after adjustment for the clinical state variables. Our data support the hypothesis that the association between helplessness/hopelessness and depression and the risk of mortality among lung cancer patients was largely confounded by the clinical state variables, including the clinical stage, PS, and severity of clinical symptoms. This hypothesis was proven, and it would reassure the cancer patients because poor psychological states in cancer patients were merely a consequence of illness but not a determinant of poor prognosis.

Acknowledgements

This study was supported by a Grant-in-Aid for cancer research for the 3rd Term Comprehensive Ten-Year Strategy for Cancer Control (H16-3jigan-010) from the Ministry of Health, Labour and Welfare, Japan. We would like to express special thanks to Toyoko Matsumoto and Fumiko Koh for collecting and filing all the data for this project. We would also wish to thank Yuko Kojima and Nobue Taguchi of the Psycho-Oncology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Japan, for their research assistance.

References

1. Derogatis LR, Morrow GR, Fetting J *et al.* The prevalence of psychiatric disorders among cancer patients. *J Am Med Assoc* 1983;**249**:751–757.
2. Uchitomi Y, Mikami I, Nagai K *et al.* Depression and psychological distress in patients during the year curative resection of non-small-cell lung cancer. *J Clin Oncol* 2003;**21**:69–77.
3. Montazeri A, Milroy R, Hole D, McEwen J, Gillis CR. Anxiety and depression in patients with lung cancer before and after diagnosis: findings from a population in Glasgow, Scotland. *J Epidemiol Community Health* 1998;**52**:203–204.
4. Hughes JE. Depressive illness and lung cancer: II. Follow-up of inoperable patients. *Eur J Surg Cancer* 1985;**11**:21–24.
5. Ginsburg ML, Quirt C, Ginsburg AD, MacKillop WJ. Psychiatric illness and psychosocial concerns of patients with newly diagnosed lung cancer. *Can Med Assoc J* 1995;**152**:701–708.
6. Hopwood P, Stephens RJ. Depression in patients with lung cancer: prevalence and risk factors derived from quality-of-life data. *J Clin Oncol* 2000;**18**:893–903.
7. Akechi T, Okamura H, Nishiwaki Y, Uchitomi Y. Psychiatric disorders and associated and predictive factors in patients with unrespectable nonsmall cell lung carcinoma. *Cancer* 2001;**92**:2609–2622.
8. Greer S, Morris T, Pettingale K. Psychological response to breast cancer: effect on outcome. *Lancet* 1979;**ii**: 785–787.
9. Molassiotis A, Van Den Akker OB, Milligan DW, Goldman JM. Symptom distress, coping style and biological variables as predictors of survival after bone marrow transplantation. *J Psychosom Res* 1997;**42**: 275–285.
10. Watson M, Haviland JS, Greer S, Davidson J, Bliss JM. Influence of psychological response on survival in breast cancer: a population-based cohort study. *Lancet* 1999;**354**:1331–1336.
11. Faller H, Bülzebruck H, Drings P, Lang H. Coping, distress, and survival among patients with lung cancer. *Arch Gen Psychiatry* 1999;**56**:756–762.
12. Faller H, Schmidt M. Prognostic value of depressive coping and depression in survival of lung cancer patients. *Psycho-Oncology* 2004;**13**:359–363.
13. Buccheri G. Depressive reactions to lung cancer are common and often followed by a poor outcome. *Eur Respir J* 1998;**11**:173–178.
14. Derogatis LR, Abeloff MD, Melisaratos N. Psychological coping mechanisms and survival time in metastatic breast cancer. *J Am Med Assoc* 1979;**242**:1504–1508.
15. Visser MRM, Smets EMA. Fatigue, depression and quality of life in cancer patients: how are they related? *Support Care Cancer* 1998;**6**:101–108.
16. Sarna L, Padilla G, Holmes C *et al.* Quality of life of long-term survivors of non-small-cell lung cancer. *J Clin Oncol* 2002;**20**:2920–2929.
17. Petticrew M, Bell R, Hunter D. Influence of psychological coping on survival and recurrence in people with cancer: systematic review. *Br Med J* 2002;**325**: 1066–1075.
18. Levy S, Herberman R, Lippman M, d'Angero T. Correlation of stress factors with sustained depression of natural killer cell activity and predicted prognosis in patients with breast cancer. *J Clin Oncol* 1987;**5**: 348–353.
19. Pettingale KW, Philalithis A, Tee DE, Greer HS. The biological correlates of psychological responses to breast cancer. *J Psychosom Res* 1981;**25**:453–458.

20. Colleoni M, Mandala M, Peruzzotti G *et al.* Depression and degree of acceptance of adjuvant cytotoxic drugs. *Lancet* 2000;**356**:1326–1327.
21. Tanaka K, Akechi T, Okuyama T, Nishiwaki Y, Uchitomi Y. Factors correlated with dyspnea in advanced lung cancer patients: organic causes and what else? *J Pain Symptom Manage* 2002;**23**:490–500.
22. Herndon 2nd JE, Fleishman S, Kornblith AB, Kosty M, Green MR, Holland J. Is quality of life predictive of the survival of patients with advanced nonsmall cell lung carcinoma? *Cancer* 1999;**85**:333–340.
23. Efficace F, Bottomley A, Smit EF *et al.* Is a patient's self-reported health-related quality of life a prognostic factor for survival in non-small-cell lung cancer patients? A multivariate analysis of prognostic factors of EORTC study 08975. *Ann Oncol* 2006;**17**:1698–1704.
24. Nakaya N, Goto K, Saito-Nakaya K *et al.* The Lung Cancer Database Project at the National Cancer Center, Japan: study design, corresponding rate, and profiles of cohort. *Jpn J Clin Oncol* 2006;**36**:280–284.
25. Hosokawa T, Ohyama M. Reliability and validity of the Japanese version of the short form Eysenck Personality Questionnaire-Revised. *Psychol Rep* 1993;**72**:823–832.
26. Akechi T, Fukue-Saeki M, Kugaya A *et al.* Psychometric properties of the Japanese version of the Mental Adjustment to Cancer (MAC) scale. *Psycho-Oncology* 2000;**9**:395–401.
27. Kitamura T. Hospital Anxiety and Depression Scale. *Seisinka Sindangaku* 1993;**4**:371–372 (in Japanese).
28. Oken MM, Creech RH, Tormey DC *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;**5**:649–655.
29. Eysenck HJ, Eysenck SBG. *Manual of the Eysenck Personality Questionnaire (Adult and Junior)* Hodder & Stoughton: London (UK), 1975.
30. Watson M, Greer S, Young J *et al.* Development of a questionnaire measure of adjustment to cancer: the MAC scale. *Psychol Med* 1988;**18**:203–209.
31. Zigmond AS, Snaith RP. The Hospital and Depression Scale. *Acta Psychiatr Scand* 1983;**67**:361–370.
32. Rothman KJ, Greenland S. *Modern Epidemiology* (2nd edn). Lippincott-Raven: Philadelphia, PA, 1998; 359–399.
33. Cody M, Nichols S, Brennan C *et al.* Psychosocial factors and lung cancer prognosis. *Psycho-Oncology* 1994;**3**:141.
34. Nakaya N, Saito-Nakaya K, Akizuki N *et al.* Depression and survival in patients with non-small cell lung cancer after curative resection: a preliminary study. *Cancer Sci* 2006;**97**:199–205.
35. Nicklasson M, Bergman B. Validity, reliability and clinical relevance of EORTC QLQ-C30 and LC13 in patients with chest malignancies in a palliative setting. *Qual Life Res* 2007;**16**:1019–1028.

Psycho-Oncology
Psycho-Oncology **17**: 154–160 (2008)
Published online 27 April 2007 in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/pon.1213

Clinical experience of the use of a pharmacological treatment algorithm for major depressive disorder in patients with advanced cancer

Masako Okamura[1], Nobuya Akizuki[2], Tomohito Nakano[1], Ken Shimizu[1], Tatsuhiko Ito[2], Tatsuo Akechi[3] and Yosuke Uchitomi[2]*

[1] *Psychiatry Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan*

[2] *Psycho-Oncology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa 277-8577, Japan*

[3] *Department of Psychiatry, Nagoya City University Medical School, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan*

Correspondence to: Psycho-Oncology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa 277-8577, Japan. E-mail: yuchitom@east.ncc.go.jp

Received: 3 August 2006
Revised: 7 March 2007
Accepted: 12 March 2007

Abstract

The objective of this study was to describe the applicability and the dropout of the pharmacological treatment algorithm for major depressive disorder in patients with advanced cancer.

Psychiatrists treated major depressive disorder in advanced cancer patients on the basis of the algorithm. For discussing the problems related to the algorithm, we reviewed the reasons for the non-application of the algorithm and the reasons for dropout of patients within a week of initiation of treatment.

The algorithm was applied in 54 of 59 cases (applicability rate, 92%). The reasons for the non-application of the algorithm were as follows: the need to add a benzodiazepine to an antidepressant in 4 cases and the need to choose alprazolam despite the depression being moderate in severity, in order to obtain a rapid onset action and reduce anxiety in a patient with short prognosis. Nineteen of the 55 patients dropped out within a week of initiation of treatment based on the algorithm. Delirium was the most frequent reason for dropout.

The applicability rate was high, but several problems were identified, including those related to the combination of antidepressants and benzodiazepines, pharmacological treatment of depression in patients with short prognosis, and delirium due to antidepressants.

Keywords: algorithm; major depressive disorder; advanced cancer; antidepressant; clinical experience

Introduction

Major depressive disorder is the most distressing psychiatric disorder in advanced cancer patients. Although the prevalence of major depressive disorder in the community is 3–4% [1], it rises to 5–26% in advanced cancer patients [2]. Several studies have indicated that depression can have a serious negative impact on the quality of life of patients with advanced cancer [3,4], causing severe suffering [5], and a desire for early death [6,7], or suicide [8], as well as psychological distress to the family members [9].

While pharmacological treatment is important in depression, advanced cancer patients have some characteristics that can influence the pharmacological treatment of depression. For instance, advanced cancer patients also have various somatic symptoms and physically compromised conditions [10,11], so the minimal deleterious effects of medication can be serious in these patients. Also there are often problems related to the drug delivery routes [12], and rapid onset of effects of the antidepressants is required in patients with a poor prognosis. Although a standard strategy has long been desired for the treatment of major depression in cancer patients, few controlled clinical studies have been conducted in this population [13–20]. In particular, there are very few studies on patients with advanced cancer, and few appropriate guidelines are available for the treatment of depression in this patient population. Though there is no pharmacological treatment algorithm for depression in this population, generally algorithms are a good idea and not only provide the framework for vast amounts of information, but can also shape the database in response to certain clinical questions around disease management or utilization of medical procedures. The several reasons why algorithms have grown in popularity include the following: reduced unnecessary variation in clinical practice

patterns; the facilitation clinical decisions; the ability to make clinical decisions explicit; and improvement the quality of treatment [21]. Furthermore, physicians may be unfamiliar about treatment of depression [22] and are not trained to treat it, and psychiatrists do not have much clinical experience and knowledge of evidence about depression among cancer patients. Thus, a pharmacological treatment algorithm for depression in cancer patients, which is based on evidence and expert opinion, is useful.

We have developed a pharmacological treatment algorithm for major depressive disorder in advanced cancer patients [23], and have used the revised version of the algorithm in clinical practices since August 2002. The objective of this study was to describe the applicability of this algorithm, the dropout rate, and the reasons for the choice of antidepressants within the framework of the algorithm and for dropout cases in this patient population. Problems related to the use of this algorithm are also identified and discussed.

Methods

Patients

This study was conducted by means of a retrospective chart review. The subjects of this study were cancer patients referred to the Psychiatry Division of the National Cancer Center Hospital (NCCH) and the Psycho-Oncology Division of the National Cancer Center Hospital East (NCCHE), Japan, between August 2002 and October 2003. The eligibility criteria for review were as follows: patients with advanced cancer, including clinical stage III or IV; patients with recurrent and systemic cancer; patients 18 years of age or older; patients diagnosed to have major depressive disorder based on the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV); and patients considered to be a suitable candidate for pharmacotherapy of depression as determined by consultation-liaison psychiatrists. Patients already prescribed drugs in the algorithm for the current episode were excluded. Since this study was a retrospective review of using the algorithm in clinical practices, written consent and institutional review board approval were not obtained.

Treatment algorithm for major depressive disorder in advanced cancer patients

The algorithm is shown in Appendix [23]. It was developed on the basis of a systematic review of the literature, our own clinical experience, and advice from consultation-liaison psychiatrists. We assessed the feasibility [24], and developed a revised version taking into consideration the problems identified during the feasibility study and updated evidence. The algorithm was designed to determine the most appropriate medication for first administration, according to the severity of depression. The treatment course was determined by the drug delivery route. If the patients could not take medicines orally, amitriptyline or clomipramine, which were approved in Japan for parenteral administration, was administered. (Parenteral preparations of amitriptyline were withdrawn from the market in 2003.) Alprazolam and methylphenidate, which have a rapid onset of action, were available for mild depression. Antidepressants for moderate and severe depression were chosen based on the profiles of adverse effects of the drugs and drug interactions, for the following three reasons. First, while the drugs do not differ significantly in terms of their antidepressant efficacy, their adverse effect profiles differ among the various classes of antidepressants (e.g. serotonin re-uptake inhibitors (SSRIs): nausea, diarrhea, etc., tricyclic antidepressants (TCAs): dry mouth, constipation, etc.). Second, as advanced cancer patients also have various somatic symptoms and a compromised general condition, even minimal deleterious effects of medications can be serious. Third, advanced cancer patients take several medications. As there is no evidence yet that a combination of antidepressants is more effective than a single agent, and compliance and drug interaction are also an important consideration, this algorithm was based on the premise of monotherapy. Every drug was started at its low dose initially, with the dose being increased gradually thereafter, while watching carefully for the development of any adverse events.

Method

The applicability of the algorithm was estimated by calculating the proportion of patients for whom the algorithm was actually applied. Consultation-liaison psychiatrists treated major depressive disorder in eligible patients on the basis of the algorithm. The antidepressants were chosen according to the algorithm, in combination with appropriate psychosocial interventions and recommended physical symptom management. Psychosocial interventions mainly consist of psychotherapy and family support. These interventions and recommendations for physical symptom management are from the point of view of depression management. Psychotherapy is individualized and modified for each patient. The fundamental element of supportive psychotherapy consists of active listening with supportive verbal intervention and the occasional interpretation. Cognitive-behavioral interventions, such as relaxation and distraction with pleasant imagery are also used. For patients who feel anxious or hopeless due

DOI: 10.1002/pon

to misunderstanding, a psycho-educational approach with realistic assurance is used [25]. Physical symptoms such as pain and fatigue are closely associated with depression. If we judge how a patient's physical symptoms affect depression, we recommend the primary physician to control the symptom, or sometimes to consult a specialist.

All the psychiatrists conducted weekly meetings to discuss the eligible patients and the implementation of the algorithm. We reviewed the reasons for non-application of the algorithm, the details of the treatment including the names of the drugs selected, dosage, drug delivery route, the reasons for the choice of the drug, and the reasons for any changes.

If the observation of a patient was interrupted, the reason was reviewed. Dropout was defined as discontinuation of the antidepressant within a week of initiation of treatment. If the reason for the dropout was the development of delirium, we reviewed the organic precipitating factors for the development of delirium using the approach used by Lawlor *et al.* [26] in their prospective study of advanced cancer patients. The status of involvement of each precipitating factor was classified as 'probable', 'possible', and 'comorbidity'. The most considerable precipitating factor of delirium was classified as 'probable'.

In an attempt to identify and discuss the problems associated with the implementation of the algorithm, we reviewed the reasons for non-application of the algorithm and also the reasons of dropout of patients from the treatment initiated based on the algorithm.

To identify the patient characteristics, we reviewed the computerized psychiatric consultation referral database of the Psychiatry and Psycho-Oncology Division of National Cancer Center, which included demographic variables (age, sex, marital status, education, and employment status) and medical information about the patient (primary cancer site, clinical stage of cancer, pain, and performance status as defined by Eastern Cooperative Oncology Group (ECOG) which is an objective index of a patient's physical functioning, ranging from 0 (no symptoms) to 4 (bedridden)). We recorded and reviewed the clinical estimation of the prognosis of the patent by the attending physicians at the first assessment.

Results

The total number of referrals to the Psychiatry Division of NCCH and the Psycho-Oncology Division of NCCHE between August 2002 and October 2003 was 1334, including 193 patients diagnosed as having major depressive disorder. Fifty-nine patients were diagnosed to have current major depressive disorder in advanced cancer and they were assessed by psychiatrists as being suitable candidates for pharmacotherapy.

Table 1. Demographic and clinical characteristics of the subjects ($N = 59$)

Characteristic	Mean	SD	Range
Age (years)	57	11	28–79
	N	**%**	
Female	38	64	
Outpatient	19	32	
Primary tumor site			
Lung	13	22	
Stomach	9	15	
Esophagus	8	14	
Breast	7	12	
Colon	7	12	
Pancreas	5	8	
Others	10	17	
Clinical stage			
III or IV	38	64	
Recurrence	18	31	
Others[a]	3	5	
Performance status (ECOG)[b]			
0	2	3	
1	19	32	
2	14	24	
3	20	34	
4	4	7	
Pain			
Present	40	68	
Absent	19	32	
Clinically estimated prognosis			
< 1 month	9	15	
1–3 months	12	20	
3–6 months	15	25	
6 months–1 year	13	22	
> 1 year	9	15	
Unknown	1	2	

[a] This includes bile duct, liver, skin, thymus, liposarcoma, malignant lymphoma, and unknown primary site.
[b] ECOG: Eastern Cooperative Oncology Group.

The demographic characteristics of the subjects are presented in Table 1. The most frequent site of cancer was the lung (22%), followed by the stomach (15%). Ninety-seven percent had physical impairment, with a performance status score of 1 or more, and 67% had pain. The clinically estimated prognosis was less than one month in 15% of the patients.

Applicability

The algorithm was applied in 54 cases (applicability rate, 92%) (54/59) (Figure 1). Among the 26 patients with mild depression, alprazolam was chosen for 19 cases, methylphenidate for 2 cases, intravenously administered amitriptyline for 4 cases, and intravenously administered clomipramine for 1 case. Among the 26 patients with moderate depression and 2 patients with severe

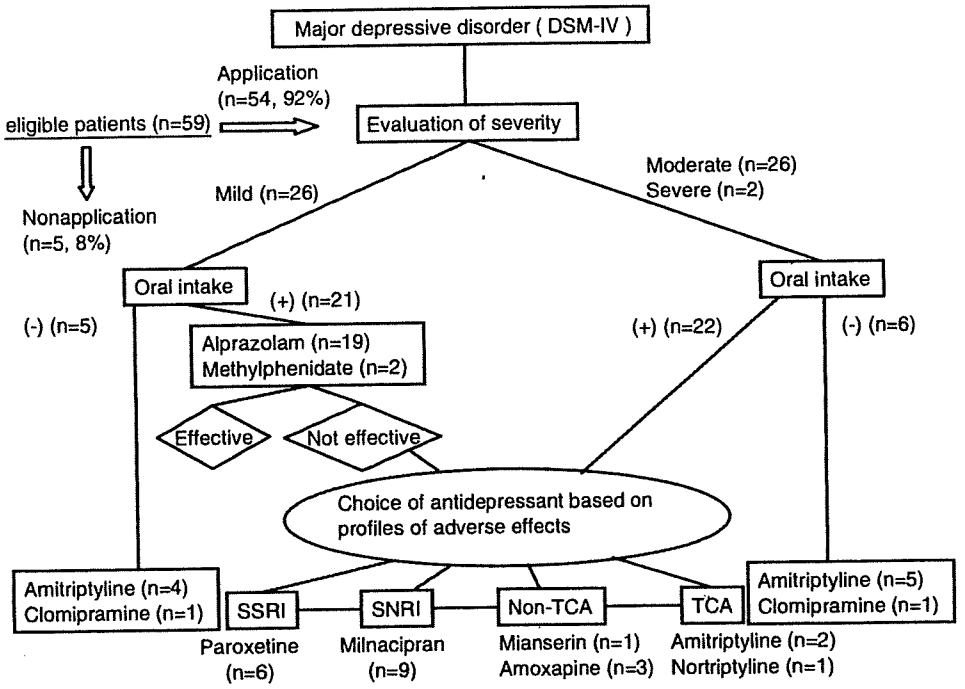


Figure 1. Pharmacological treatment algorithm for major depressive disorder in advanced cancer patients. SSRI: selective serotonin reuptake inhibitors; SNRI: serotonin noradrenalin reuptake inhibitors; TCA: tricyclic antidepressants

depression, intravenously administered amitriptyline was chosen for 5 cases, and intravenously administered clomipramine was chosen for 1 case. According to the 'choice of antidepressant based on the profiles of the adverse effects', paroxetine was chosen for 6 cases, milnacipran for 9 cases, amoxapine for 3 cases, mianserin for 1 case, nortriptyline for 1 case, and amitriptyline for 2 cases. The reasons for the selection of paroxetine were 'to prevent dry mouth and constipation' in 3 cases, 'to prevent urinary disturbances' in 2 cases, and 'to prevent delirium' in 1 case. The reasons for the selection of milnacipran were 'the presence of underlying hepatic impairment' in 3 cases, 'to prevent dry mouth and constipation' in 3 cases, and 'to prevent nausea' in 3 cases. The reasons for the selection of amoxapine were 'to prevent nausea' in 1 case, 'previously effective' in 1 case, and 'to provide an analgesic adjuvant' in 1 case. The reason for the selection of mianserin was 'to prevent arrhythmia'. The reason for the selection of nortriptyline was 'to prevent nausea' in 1 case. The reasons for the selection of amitriptyline were 'insomnia' in 1 case, and 'agitation' in 1 case. Initial doses and maximum doses are given in Table 2.

The psychiatrists did not apply the algorithm in 5 of the 59 cases. The reasons were the need to add a benzodiazepine to an antidepressant in 4 cases and the need to choose alprazolam, in spite of the diagnosis of moderate depression in order to obtain a rapid onset of action and reduce the anxiety of the patient in a case with a short prognosis. Of these 5 patients, 4 patients had moderate depression and 1 had severe depression. Because of high-anxiety level and agitation, we used antidepressants concomitantly with benzodiazepines in 4 cases.

Table 2. Initial and maximum doses ($N = 54$)

	N	Initial dose (mg)		Maximum dose (mg)	
		Median	Range	Median	Range
Mild cases					
Alprazolam	19	0.8	0.4–1.2	1.2	0.4–2.4
Methylphenidate	2	5	5	5	5
Amitriptyline[a]	4	10	5–10	12.5	10–15
Clomipramine[a]	1	6.25	6.25	6.25	6.25
Moderate and severe cases					
Milnacipran	9	30	15–50	30	15–100
Paroxetine	6	10	5–10	10	5–20
Amoxapine	3	25	25–75	25	25–75
Amitriptyline	2	25	20–30	30	30
Nortriptyline	1	10	10	10	10
Mianserin	1	10	10	10	10
Amitriptyline[a]	5	10	5–10	10	10–25
Clomipramine[a]	1	6.25	6.25	6.25	6.25

[a] Parenteral administration.

Dropout within a week

Nineteen of the 54 patients dropped out within a week of the start of treatment initiated based on the

algorithm: 8 manifested delirium; 3 showed deterioration of the general physical condition due to cancer; 2 showed adverse effects of the antidepressant treatment (fatigue after administration of milnacipran in 1 case and nausea after administration of paroxetine in one case); 2 were transferred to other hospitals; 1 showed resistance to the antidepressants; 1 suffered a brain hemorrhage; and 2 discontinued the treatment for unknown reasons. The antidepressants (alprazolam in 3 cases, amitriptyline in 1 case, and amoxapine in 1 case) were the probable precipitating factors of delirium in 5 out of the 8 cases who manifested delirium.

Discussion

In this report, we have described our experience with our algorithm-based pharmacological treatment of major depressive disorder designed especially for advanced cancer patients.

The applicability of the algorithm was 92%. This was adequate in view of the physical condition of the advanced cancer patients. As advanced cancer patients often have a wide range of physical symptoms, including pain, fatigue, weakness, anorexia, dry mouth, constipation, and nausea [10,11], some of which may limit the use of antidepressants, even minimal deleterious effects of medication can be serious in these patients. So we selected the antidepressant according to the profiles of adverse effects of the drugs for cases of moderate and severe depression. The physical symptoms and state, such as the potential development of dry mouth, constipation, urinary disturbances, nausea, delirium, hepatic impairment, and arrhythmia, were considered for the choice of the drug. Some other considerations in the choice of antidepressants were relief of symptoms such as insomnia, agitation, and pain.

As for the 11 cases which could not take medicine orally, amitriptyline and clomipramine were administered intravenously. Since the production of amitriptyline discontinued in Japan in 2003, only clomipramine is currently available for parenteral administration; therefore, such patients with depression are becoming more difficult to treat. While citalopram (SSRI), doxepin (TCA), and other antidepressants are available for intravenous administration in other countries [27], development of parenterally administrated antidepressants is needed in Japan.

In 4 cases, the algorithm was not applied because of the need to add a benzodiazepine to the antidepressant. As there was no evidence that a combination of some antidepressants was more effective than a single agent alone, and compliance and drug interaction were also important considerations, our algorithm was based on the premise of monotherapy. A previous meta-analysis revealed that the improvement of depression was more likely in the antidepressant–benzodiazepine combination group than in the antidepressant alone group at 4 weeks, but that the difference was no longer significant at 6 or 8 weeks [28]. In addition, the patients allocated to the combination group were less likely to dropout from the treatment due to the side effects than those receiving antidepressants alone [28]. Thus, the antidepressant–benzodiazepine combination may be considered in patients with high anxiety and agitation, or when dropout needs to be avoided.

In one case, the algorithm was not applied because of the selection of alprazolam in spite of the patient having moderate depression, in order to obtain a rapid onset action and reduce the anxiety for the patient who had a short prognosis. This is an issue that must be considered in the pharmacological treatment of patients with a short prognosis. It would be too difficult to conduct a randomized controlled trial of antidepressants for such a population, and there are only a few review articles and case reports [29–34]. In these reports, while no recommendations were made on the pharmacological treatment, it was suggested that psychostimulants may possibly have an effect and that alternative treatments with benzodiazepines and neuroleptics may be considered.

Delirium was the most frequent reason for dropout, and the antidepressants were the probable precipitating factor in 5 of the 8 cases. As delirium occurs in most terminally ill patients [26], it may be difficult to entirely prevent delirium based on the choice of pharmacological treatment of depression. It is known that TCAs sometimes induce delirium [35], and that benzodiazepines, including alprazolam, can also induce delirium. Therefore, the physical state should be assessed carefully, and the use of TCAs and bezodiazepines should be avoided in patients who are very vulnerable in terms of their physical condition and at a high risk of delirium. Though the reasons for the selection of amitriptyline were 'insomnia' in 1 case, and 'agitation' in 1 case, a combination of SSRI and neuloleptics may be a more safe way to treat such cases. Only clomipramine is available for parenteral administration currently, therefore, other antidepressants for parenteral administration are needed in Japan. Two patients dropped out because of the adverse effects of antidepressants. It was considered that dropouts due to adverse effects of antidepressants were few because the antidepressants were chosen based on the profiles of their adverse effects and drug interactions.

The applicability rate is high, but several problems related to the use of the algorithm were identified. Certain aspects require modification. The first issue is related to the combined use of antidepressants and benzodiazepines. The second

issue is pharmacological treatment of depression in patients with a short prognosis. The third issue is the development of delirium as an effect of the antidepressants. We are revising and developing the algorithm based on these considerations.

Appendix: Pharmacological treatment algorithm for major depressive disorder in patients with advanced cancer

Line 1

The diagnosis of major depressive disorder in patients with advanced cancer is based on the DSM-IV criteria. They include physical symptoms such as loss of appetite, insomnia, and loss of energy if they exist, whether the cause is depression, the treatment for cancer, or the cancer itself.

Line 2

Treatment is based on the severity of major depressive disorder. Cases are differentiated into mild and moderate to severe.

Line 3

The drug delivery route is evaluated. The presence of any intestinal obstruction or dysfunction of deglutition is a hindrance to oral administration.

Line 4

As rapid onset of the antidepressant effect is required with a poor prognosis, alprazolam and psychostimulants are the first choice for mild cases. Alprazolam is recommended for patients with anxiety and agitation, and psychostimulants are recommended for patients with somnolence and fatigue.

Line 5

Efficacy and adverse effects are evaluated by observation up to a week.

Line 6

Patients with advanced cancer have various physical symptoms and compromised conditions, and take several medications. So an antidepressant is chosen based on profiles of adverse effects and drug interactions.

Line 7

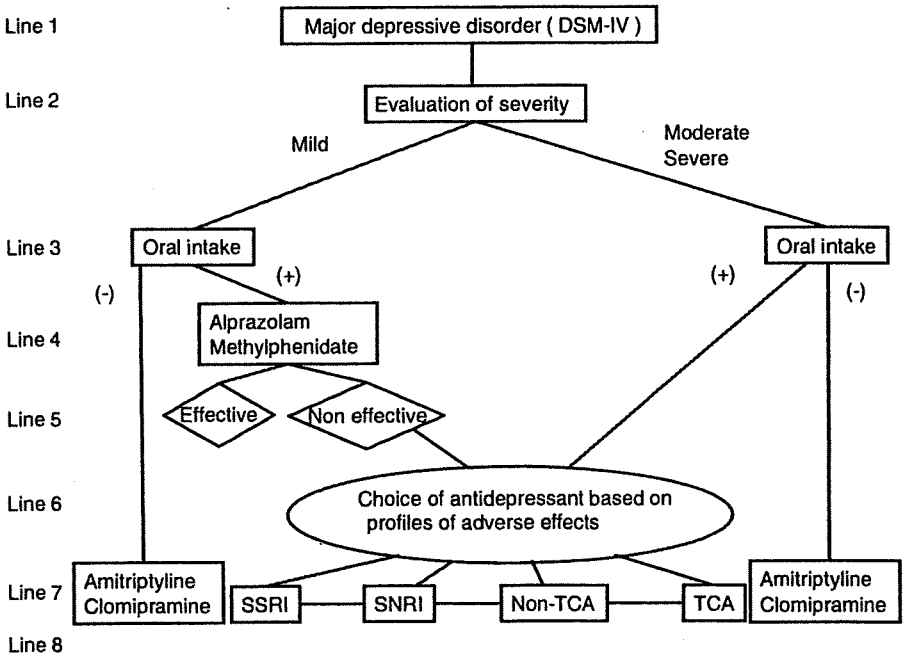
As there is no evidence yet that a combination of antidepressants is more effective than a single agent, and compliance and drug interaction are also an important consideration, this algorithm was based on the premise of monotherapy.

For patients who are unable to take medicine orally, clomipramine or amitriptyline, which are approved in Japan for parenteral administration, is administered.

SSRIs are recommended, except for patients with gastrointestinal symptoms such as nausea and a problem of drug interaction. SNRIs are recommended for patients with liver dysfunction and a problem of drug interaction, and when anticholinergic effects should be avoided. It is difficult to administer TCAs for patients with dry mouth, constipation, and fatigue which are similar symptoms as anticholinergic effects, but TCAs are recommended for agitated patients. As non-TCAs do not have the same specific effect, they should be used depending on each effect.

Line 8

Give every medication at a low dosage initially and increase it gradually, observing carefully for any adverse effects.



Acknowledgements

We are grateful to Ms Y. Kojima, RN, and Ms R. Katayama of the Psycho-Oncology Division, National Cancer Center Hospital East, for their research assistance. This study was supported in part by a Grant-in-Aid for Nervous and Mental Disorders and a Grant-in-Aid for Cancer Research of the Japanese Ministry of Labor, Health and Welfare.

References

1. Waraich P, Goldner EM, Somers JM, Hsu L. Prevalence and incidence studies of mood disorders: a systematic review of the literature. *Can J Psychiatry* 2005;**49**:124–138.
2. Hotopf M, Chidgey J, Addington-Hall J, Ly KL. Depression in advanced disease: a systematic review Part 1. Prevalence and case finding. *Palliat Med* 2002; **16**:81–97.
3. Grassi L, Indelli M, Marzola M *et al.* Depressive symptoms and quality of life in home-care-assisted cancer patients. *J Pain Symptom Manage* 1996;**12**: 300–307.
4. Okamura M, Yamawaki S, Akechi T, Taniguchi K, Uchitomi Y. Psychiatric disorders following first breast cancer recurrence: prevalence, associated factors and relationship to quality of life. *Jpn J Clin Oncol* 2005;**35**:302–309.
5. Cherny NI, Coyle N, Foley KM. Suffering in the advanced cancer patient: a definition and taxonomy. *J Palliat Care* 1994;**10**:57–70.
6. Breitbart W, Rosenfeld B, Pessin H *et al.* Depression hoplessness, and desire for hastened death in terminally ill patients with cancer. *J Am Med Assoc* 2000;**284**: 2907–2911.
7. Chochinov HM, Wilson KG, Enns M *et al.* Desire for death in the terminally ill. *Am J Psychiatry* 1995;**152**:1185–1191.
8. Henriksson MM, Isometsa ET, Hietanen PS, Aro HM, Lonnqvist JK. Mental disorders in cancer suicides. *J Affect Disord* 1995;**36**:11–20.
9. Cassileth BR, Lusk EJ, Strouse TB, Miller DS, Brown LL, Cross PA. A psychological analysis of cancer patients and their next-of-kin. *Cancer* 1985;**55**:72–76.
10. Conill C, Verger E, Henriquez I *et al.* Symptom prevalence in the last week of life. *J Pain Symptom Manage* 1997;**14**:328–331.
11. Vainio A, Auvinen A. Prevalence of symptoms among patients with advanced cancer: an international collaborative study. Symptom Prevalence Group. *J Pain Symptom Manage* 1996;**12**:3–10.
12. Ripamonti C. Management of bowel obstruction in advanced cancer patients. *J Pain Symptom Manage* 1994;**9**:193–200.
13. Costa D, Mogos I, Toma T. Efficacy and safety of mianserin in the treatment of depression of women with cancer. *Acta Psychiatr Scand* 1985;**72**:85–92.
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 Clin Oncol* 2003;**21**:1937–1943.
15. Heeringen KV, Zivkov M. Pharmacological treatment of depression in cancer patients. A placebo-controlled study of mianserin. *Br J Psychiatry* 1996;**169**:440–443.
16. Holland JC, Romano SJ, Heiligenstein JH, Tepner RG, Wilson MG. A controlled trial of fluoxetine and desipramine in depressed women with advanced cancer. *Psycho-Oncology* 1998;**7**:291–300.
17. Morrow GR, Hickok JT, Roscoe JA *et al.* 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* 2003;**21**:4635–4641.
18. Pezzella G, Moslinger-Gehmayr R, Contu A. Treatment of depression in patients with breast cancer: a comparison between paroxetine and amitriptyline. *Breast Cancer Res Treat* 2001;**70**:1–10.
19. Razavi D, Allilaire JF, Smith M *et al.* The effect of fluoxetine on anxiety and depression symptoms in cancer patients. *Acta Psychiatr Scand* 1996;**94**:205–210.
20. Roscoe JA, Morrow GR, Hickok JT *et al.* Effect of paroxetine hydrochloride (Paxil) on fatigue and depression in breast cancer patients receiving chemotherapy. *Breast Cancer Res Treat* 2005;**89**:243–249.
21. Gilbert DA, Altshuler KZ, Rago WV *et al.* Texas medication algorithm project: definitions, rationale, and methods to develop medication algorithms. *J Clin Psychiatry* 1998;**59**:345–351.
22. Chochinov HM. Depression in cancer patients. *Lancet Oncol* 2001;**2**:499–505.
23. Akizuki N, Akechi T, Nakano T, Okamura M, Uchitomi Y. Major depression in advanced cancer patients. In *Pharmacological Treatment Algorithms for Affective Disorders*, Motohashi N (ed.). Jiho: Tokyo, 2003; 83–99.
24. Akizuki N, Okamura H, Akechi T *et al.* Clinical experience of the pharmacological treatment algorithm for major depression in advanced cancer patients: preliminary study. *Int J Psychiatry Clin Pract* 2002; **6**:83–89.
25. Wilson KG, Chochinov HM, Faye BJd, Breitbart W. Diagnosis and Management of Depression in Palliative Care. In *Handbook of Psychiatry in Palliative Medicine*, Chochinov HM, Breitbart W (eds). Oxford: New York, 2000; 25–49.
26. Lawlor PG, Gagnon B, Mancini IL *et al.* Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. *Arch Intern Med* 2000;**160**:786–794.
27. Moukaddam NJ, Hirschfeld RM. Intravenous antidepressants: a review. *Depress Anxiety* 2004;**19**:1–9.
28. Furukawa TA, Streiner DL, Young LT. Is antidepressant-benzodiazepine , combination therapy clinically more useful? A meta-analytic study. *J Affect Disord* 2001;**65**:173–177.
29. Block SD. Assessing and managing depression in the terminally ill patient. *Ann Intern Med* 2000;**132**:209–218.
30. Homsi J, Walsh D, Nelson KA, LeGrand S, Davis M. Methylphenidate for depression in hospice practice: a case series. *Am J Hosp Palliat Care* 2000;**17**:393–398.
31. Kugaya A, Akechi T, Nakano T, Okamura H, Shima Y, Uchitomi Y. Successful antidepressant treatment for five terminally ill cancer patients with major depression, suicidal ideation and desire for death. *Support Care Cancer* 1999;**7**:432–436.
32. Lloyd-Williams M. Difficulties in diagnosing and treating depression in the terminally ill cancer patient. *Postgrad Med J* 2000;**76**:555–558.
33. Macleod AD. Methylphenidate in terminal depression. *J Pain Symptom Manage* 1998;**16**:193–198.
34. Stiefel F, Die Trill M, Berney A, Olarte JM, Razavi D. Depression in palliative care: a pragmatic report from the Expert Working Group of the European Association for Palliative Care. *Support Care Cancer* 2001; **9**:477–488.
35. Degner D, Grohmann R, Kropp S *et al.* Severe adverse drug reactions of antidepressants: results of the German multicenter drug surveillance program AMSP. *Pharmacopsychiatry* 2004;**37**(Suppl 1):S39–S45.