HOKKAIDO UNIVERSITY

Title	Long-term outcome of antidepressant-refractory depression: The relevance of unrecognized bipolarity
Author(s)	Inoue, Takeshi; Nakagawa, Shin; Kitaichi, Yuji; Izumi, Takeshi; Tanaka, Teruaki; Masui, Takuya; Kusumi, Ichiro; Denda, Kenzo; Koyama, Tsukasa
Citation	Journal of Affective Disorders, 95(1-3), 61-67 https://doi.org/10.1016/j.jad.2006.04.020
Issue Date	2006-10
Doc URL	http://hdl.handle.net/2115/30350
Type	article (author version)
File Information	inoue_takeshi.pdf

Instructions for use

Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP

Long-term outcome of antidepressant-refractory depression: the relevance of unrecognized bipolarity

Takeshi Inoue*, Shin Nakagawa, Yuji Kitaichi, Takeshi Izumi, Teruaki Tanaka, Takuya Masui, Ichiro Kusumi, Kenzo Denda, Tsukasa Koyama

Department of Psychiatry, Hokkaido University Graduate School of Medicine, North 15, West 7, Kita-ku, Sapporo 060-8638, Japan

*Corresponding author:

Takeshi Inoue, MD, PhD

Department of Psychiatry, Neural Function

Hokkaido University Graduate School of Medicine

North 15, West 7, Sapporo 060-8638, Japan

Phone: +81-11-706-5160

Fax: +81-11-706-5081

E-mail: tinoue@med.hokudai.ac.jp

Abstract

Background: The long-term outcome of antidepressant-refractory depression is not well known. Therefore, the present study investigated the long-term outcome of 26 antidepressant-refractory patients with depression, whom we had studied and treated in 1995.

Methods: Before being classified as nonresponse, these patients had been treated adequately with at least two tricyclic or heterocyclic antidepressants (a minimum of the equivalent of 150 mg of imipramine for 4 weeks). In 1995, 21 of 26 patients were diagnosed with unipolar depression while 5 were diagnosed with bipolar depression. Mean follow up was 5.7 years (range, 1-7 years) and changes in diagnosis, remission, and treatment efficacy were evaluated.

Results: Following the long-term follow-up, 13 patients achieved full remission and demonstrated high social functioning (mean GAF score, 91). A further 4 depressed patients experienced full remission; however, subsequent recurrence was observed. In total, 17 of 26 patients experienced remission at least once during the long-term follow-up period despite the chronic depressive episodes observed at study entry. Adjuvant treatment with lithium, dopamine receptor agonists, or thyroid hormone was effective for promoting full remission. Among the 21 patients initially diagnosed with unipolar depression in 1995, diagnoses were changed to bipolar depression in 5 cases.

Limitations: This naturalistic study had a relatively small sample size and treatment was not controlled.

Conclusions: Long-term follow-up revealed that a substantial proportion of antidepressant-refractory depression is comprised of bipolar disorders. In addition,

augmentation therapies are effective for promoting full remission among chronically depressed patients without a risk of serious side effects.

Key Words: antidepressant-refractory depression, antidepressant-resistant depression, mood disorder, augmentation therapy, lithium, dopamine receptor agonist

1. Introduction

Antidepressants are clearly beneficial in the treatment of major depression. However, response rates to a variety of antidepressants (classified by more than 50% reduction in depression rating scales) are generally 60-70% (Thase and Rush, 1995; Janicak et al., 2002). However, the remaining 30-40% of patients do not sufficiently improve, even if they take the adequate or maximum doses of antidepressants for a sufficient period of time (i.e., a minimum of the equivalent of 150 mg of imipramine for 4 weeks). Half of depressed patients who are non-responders to their first antidepressant may respond following a change to a second antidepressant (typically a drug with a different pharmacological profile) or a pharmacologically reasonable combination therapy consisting of two antidepressants (Thase and Rush, 1995; Lam et al., 2002). Despite multiple pharmacological interventions, 5-10% of patients remain depressed (Inoue et al., 2002). Depressed patients, who are treatment-resistant (or refractory) to multiple, adequate antidepressant treatments, have been widely observed and extensively studied during the last two decades (Thase and Rush, 1995; Stimpson et al., 2002).

As indicated by Roose (1990), the most important issue in treatment-resistant depression is its definition. The term "(antidepressant) treatment-resistant depression" should be applied to patients who do not respond to an antidepressant given in adequate amount for a sufficient duration (Roose, 1990; Halpern and Glassman, 1990), and should be distinguished from intolerant patients, who are unable to tolerate an adequate dose of an antidepressant due to adverse effects, and non-compliant patients; these latter two cases are referred to as pseudorefracotry depression (Möller, 1992). Thase and Rush (1995) defined "(antidepressant) treatment-refractory depression" as treatment

nonresponse (i.e., persistence of significant depressive symptoms) despite at least two treatment trials with drugs from different pharmacological classes, each used in an adequate dose for a sufficient period of time (Thase and Rush, 1995). This definition is reasonable because clinical findings suggest that 20-70% of nonresponders will respond to a different type of antidepressant (Thase and Rush, 1995). However, most studies on antidepressant-resistant depression or antidepressant-refractory depression have investigated depressed patients who had not responded to only one adequate antidepressant treatment (for a review see Thase and Rush, 1995; Stimpson et al., 2002). The primary reason why these studies have not investigated patients who have not responded to two or more antidepressants with different pharmacological properties is the difficulty of obtaining a large sample size as a result of this stricter definition of antidepressant-refractory depression.

The effects of augmentation therapies utilizing lithium or thyroid hormones have been studied in open trials and randomized controlled trials. The results of these studies have shown that these augmentation therapies are effective in the treatment of refractory depression during the relatively short period of the clinical trials (Thase and Rush, 1995; Stimpson et al., 2002). However, there has been no study of the long-term use of augmentation therapies for depression in naturalistic settings.

The long-term outcome and prognosis of antidepressant-refractory depression is not well known, although several clinical studies have investigated the treatment and symptomatology of antidepressant-refractory depression (Roose et al., 1986; Thase and Rush, 1995). We reported the demographic characteristics and symptoms of antidepressant-refractory depression and the efficacy of augmentation therapies (Inoue et al., 1996a). In 1995, 34 depressed patients (9 bipolar, 25 unipolar) were studied, and a

follow-up study of these patients with antidepressant-refractory depression was conducted. In the present study, outcome for antidepressant-refractory depression is reported by a prospective long-term follow-up study. To assess full remission and improvement of depression, we used the Global Assessment of Functioning (GAF) Scale (DSM-III-R) rather than the Hamilton Depression Rating Scale (HDRS).

2. Methods

2.1. Study design

The present research was a naturalistic follow-up study of antidepressant-refractory depression, including both bipolar and unipolar depressed patients. In 1995, we investigated the demographic characteristics, symptoms, and treatment responses to augmentation therapies of 34 antidepressant-refractory depressed patients (9 bipolar, 25 unipolar) (Inoue et al., 1996a). Each patient had satisfied the DSM-III-R criteria for major depression with melancholia or bipolar disorder, depressed in the current depression episode. Inclusion criteria required moderate depressed symptoms after adequate treatment with two or more antidepressants (i.e., a minimum of the equivalent of 150 mg of imipramine for 4 weeks). In 1995, tricyclic and tetracyclic antidepressants were available in Japan; however, monoamine oxidase inhibitors, serotonin-noradrenaline reuptake inhibitors, and selective serotonin reuptake inhibitors had not yet been approved. According to the Clinical Global Impressions (CGI) scale (National Institute of Mental Health, 1985), treatment efficacies were evaluated as worse, no change, minimally improved, much improved, or very much improved. Patients rated very much improved or much improved were regarded as the responders. Following the completion of this

study, these patients continued to attend our department and receive treatment. Treatment, symptoms, and social functioning were prospectively recorded for 7 years, from 1995 until 2002.

2.2. Patients

Of the subjects in our 1995 study, patients who were followed up for one or more years were enrolled in the present study. Depressed patients with brain MRI or EEG evidence of organic brain disease were excluded from the present study. Patients with concurrent significant medical problems were also excluded from the research. From the 34 patients in the 1995 study, a total of 26 patients (5 bipolar and 21 unipolar, according to the 1995 diagnoses) were investigated.

2.3. Assessment

The authors investigated the current diagnosis, severity of symptoms, medication, social functioning (employment, etc), GAF scores, whether the patients had experienced full remission for 7 years, and whether the patients had discontinued medication due to full remission. Treatment efficacies of various augmentation therapies have been evaluated according to the CGI scale (National Institute of Mental Health, 1985).

Clinical pharmacological studies often use a score of 7 or less on the 17-items HDRS (Thase and Rush, 1995) as a definition of remission; however, symptomatic improvement does not fully account for the functional recovery observed in fully remitted patients (Lenderking et al., 1999; Lecrubier, 2002). Although DSM-III-R defines full remission as "no significant signs or symptoms of the disturbance during the past 2 months", the achievement of an asymptomatic state with a full, functional recovery (i.e., a complete

recovery) has traditionally been viewed as full remission in depression and is a fundamental goal for the treatment of depression (Kraepelin, 1913; Weitbrecht, 1973; Lecrubier, 2002). Therefore, a score of 80 or higher on the GAF scale is a good and straightforward indicator of full remission.

3. Results

3.1. Diagnosis

After the mean follow-up period of 5.7 years, among the 15 patients with major depression, single episode, 1 patient was diagnosed with major depression, recurrent, 4 patients were diagnosed with bipolar disorder, while the diagnosis of the remaining 10 patients remained major depression, single episode (Tables 1A and 1B). Of 6 patients diagnosed in 1995 with major depression, recurrent, 1 patient was diagnosed with bipolar disorder, and 5 patients were diagnosed with major depression, recurrent. The 1995 diagnoses of 5 bipolar patients were not changed (Table 1A). Of the 21 unipolar depressed patients, 5 diagnoses were changed to bipolar disorder.

In 2002, the 26 subjects consisted of 10 bipolar patients, 6 patients with major depression, recurrent, and 10 patients with major depression, single episode.

3.2. Outcome

During the long-term follow-up period, we confirmed that 8 of 10 patients diagnosed with bipolar depression and 9 of 16 patients diagnosed with unipolar depression achieved full remission (Table 2A). Recurrence occurred in only 2 of 9 patients diagnosed with remitted unipolar depression, and 1 patient with recurrence remitted again; however, 1

patient had moderate depression at the final observation after two recurrences and one remission (Table 2B). Among patients diagnosed with bipolar depression, 5 of 10 experienced a recurrence of depression and 7 of 10 experienced hypomanic/manic episodes.

After the follow-up period, 13 of 26 patients (5 of 10 bipolar patients and 8 of 16 unipolar patients) finally achieved full remission and demonstrated high social functioning (mean GAF score, 91) (Tables 1A and 1B). In reality, 8 of 13 remitted patients had returned to work (3 patients as housewives) by the final observation. Among these fully remitted patients, 5 discontinued antidepressant treatment (1 bipolar patient continued to take valproic acid), and 8 remained on antidepressants, dopamine receptor agonists, or mood stabilizers (data not shown). The 4 remaining depressed patients experienced full remission but recurrence was observed thereafter. Including these patients with full remission and recurrence, 17 of 26 patients experienced full remission at least once during the follow-up period.

After the follow-up period, thirteen patients (5 bipolar, 8 unipolar) still had depression: 2 severe, 2 moderate, and 9 mild (Tables 1A and 1B). In 7 of 13 patients, depression has continued since diagnosis in 1995 despite adequate antidepressant treatment and various augmentation therapies: one moved to a different hospital because of home relocation in year 1, however, the other 6 patients now receive treatment as outpatients at our department.

3.3. Treatment

The 26 patients in this study received two or more antidepressants and various augmentation therapies. Four patients were treated with ECT, but the efficacy was

transient and all patients relapsed (data not shown). Augmentation therapies contributory to full remission were noted and shown in Tables 2A and 2B. In 9 of 13 patients with full remission at the final evaluation, the addition of dopamine receptor agonists (bromocriptine or pergolide) to adequate doses of conventional antidepressants was effective. The combination of lithium and dopamine receptor agonists with antidepressants was effective in 1 patient. The combination of lithium and L-thyroxine with antidepressants was effective in 2 patients.

All patients received lithium augmentation trials, and 4 (1 bipolar, 3 unipolar according to 1995 diagnosis) of 26 patients (15%) were lithium responders. As the diagnoses were changed after the long-term follow-up, these four patients were 3 bipolar and 1 unipolar patients at the final evaluation.

Long-term use of various augmentation therapies, such as lithium, thyroid hormone and dopamine receptor agonists, did not cause any serious side effects or any sequelae. No cases of rapid cycling were observed during the follow-up period. Among the patients in this study, the long-term use of antidepressants clearly did not cause mixed or (hypo)manic episodes.

4. Discussion

In the present study, subsequent to long-term follow-up (mean, 5.7 years, range, 1-7 years), the diagnoses of 5 (24%) of 21 patients with unipolar antidepressant-refractory depression were changed to bipolar disorder. There has been no research conducted on the conversion from unipolar depression to bipolar disorder in antidepressant-refractory depression. However, in non-refractory depression, a similar finding that 70 (12.5%) of

599 unipolar depressed patients were converted to bipolar disorder in a prospective observation period of up to 11 years was reported by Akiskal et al. (1995). In 1995, our patients had been depressed for an average of 5 years, indicating that these unipolar depressed patients were observed for an average of 11 years, a period similar to the study by Akiskal et al. (1995). In comparison to non-refractory depression, there may be more converters from unipolar to bipolar in antidepressant-refractory depression. Recommendation of more intensive use of mood stabilizers might be considered after the completion of future research. Furthermore, the increased tendency for patients diagnosed with unipolar antidepressant-refractory depression to become manic in comparison to non-refractory unipolar depression should be noted. In the end, 10 (38%) of 26 treatment-refractory depressed patients were diagnosed as bipolar at the final evaluation. This relatively high prevalence of bipolar disorder is comparable to the 46% prevalence of bipolar I and II disorders in patients with antidepressant-resistant depression recently observed by Sharma et al. (2005). As antidepressant-refractory depression includes more bipolarity, this suggests that bipolarity plays an important role in the pathophysiology of a subgroup of patients with antidepressant-refractory depression.

Patients diagnosed with depression associated with both unipolar and bipolar mood disorders are believed to be able to completely recover and achieve full remission (Kraepelin, 1913; Weitbrecht, 1973). However, in previous studies, long-term observation until full remission has not been attained. By the 1995 evaluation in the present study, patients with antidepressant-refractory depression had suffered from chronic depression for an average of 5 years, for unipolar depression, and 3.4 years, for bipolar depression. Nevertheless, during the long-term follow-up of the present study, we confirmed that 8 of

10 bipolar depressed patients and 9 of 16 unipolar depressed patients achieved full remission. While full remission of these depressed patients is likely in principle, as observed by Emil Kraepelin (1913), it is clinically important to confirm in naturalistic settings that chronic antidepressant-refractory depression is not a subgroup that is unable to achieve full remission.

During the follow-up period, recurrence occurred in only 2 of 10 remitted unipolar depressed patients, and these patients were remitted thereafter again. In bipolar depressed patients, 5 of 10 patients experienced recurrence of depression and 7 of 10 patients experienced hypomanic/manic episodes. Accordingly, as also shown in the 1995 study, bipolar antidepressant-refractory patients had more episodes than unipolar antidepressant-refractory depressed patients. The prevention of such mood episodes by mood stabilizers might be important for these bipolar antidepressant-refractory depressed patients, although they continue to have chronic episodes of depression for years. However, as half of the bipolar patients had been diagnosed with unipolar depression in 1995 because of a lack of previous manic or hypomanic episodes, they could not receive mood stabilizers until the final diagnosis was made. Therefore, the diagnosis of bipolar depression before the first manic/hypomanic episode is an important issue.

For effective treatment of refractory depression, several limitations of our study must be considered: the choice of augmentation therapies used for our patients was not controlled, and their efficacies were evaluated based on the CGI scale. Nevertheless, we can suggest that lithium, L-thyroxine, and dopamine receptor agonists, in combination with antidepressants, are effective treatments for patients with either unipolar or bipolar antidepressant-refractory depression. Meta-analyses based on placebo-controlled double-blind studies have confirmed the efficacy of lithium, but not triiodotyronine, for

refractory depression (Aronson et al., 1996; Bauer and Döpfmer, 1999). However, a systematic review indicated that even the evidence for lithium augmentation is very weak (Stimpson et al., 2002). Despite limited evidence, clinicians must pursue effective pharmacological therapies for antidepressant-refractory depression for the benefit of these patients. L-thyroxine and dopamine receptor agonists have not been investigated by randomized controlled trials for antidepressant-refractory depression, however, their efficacies were reported in open-labeled trials (Inoue et al., 1996b; Bauer et al., 1998). The present study showed that the addition of dopamine receptor agonists was effective in 9 of 13 patients with full remission as the final evaluation, the addition of lithium and a dopamine receptor agonist was effective in 1 patient, and the addition of lithium and L-thyroxine was effective in 2 patients. Accordingly, these augmentation therapies were considered helpful for these remitted patients at the final evaluations in long-term naturalistic observations without any serious side effects.

Interestingly, 1 of 4 lithium responders began the follow-up with a bipolar disorder; however, these responders consisted of 3 bipolar and 1 unipolar patients by the conclusion of the study. Previous studies have primarily examined the effect of lithium augmentation among unipolar depressed patients. However, with only a small number of bipolar depressed patients, a meta-analysis could not draw conclusion as to whether bipolar patients are more or less likely responders compared with unipolar depressed patients (Bauer and Döpfmer, 1999). Future studies should compare the response rate to lithium augmentation among unipolar and bipolar depressed patients who have been diagnosed based on long-term observation.

References

Akiskal, H.S., Maser, J.D., Zeller, P.J., Endicott, J., Coryell, W., Keller, M., Warshaw, M., Clayton, P., Goodwin, F., 1995. Switching from 'unipolar' to bipolar II. An 11-year prospective study of clinical and temperamental predictors in 559 patients. Arch. Gen. Psychiatry 52, 114-23.

Aronson, R., Offman, H.J., Joffe, R.T., Naylor, C.D., 1996. Triiodothyronine augmentation in the treatment of refractory depression. A meta-analysis. Arch. Gen. Psychiatry 53, 842-8

Bauer, M., Döpfmer, S., 1999. Lithium augmentation in treatment-resistant depression: Meta-analysis of placebo-controlled studies. J. Clin. Psychopharmacol. 19, 427-434.

Bauer, M., Hellweg, R., Gräf, K.-J., Baumgartner, A., 1998. Treatment of refractory depression with high-dose thyroxine. Neuropsychopharmacol. 18, 444-455.

Halpern, J.K., Glassman, A.H., 1990. Adequate tricyclic treatment: defining the tricyclic nonresponder. In: Roose, S.P., Glassman, A.H. (Eds.), Treatment Strategies for Refractory Depression. American Psychiatric Press, Washington, DC, pp. 11-32.

Inoue, T., Izumi, T., Honma, Y., Ohmori, T., Denda, K., Kasahara, T., Koyama, T., 1996a. Survey and treatment strategy of antidepressant-resistant depression. Psychiatria et Neurologia Japonica 98, 329-342. (in Japanese)

Inoue, T., Tsuchiya, K., Miura, J., Sakakibara, S., Denda, K., Kasahara, T., Koyama, T., 1996b. Bromocriptine treatment of tricyclic and heterocyclic antidepressant-resistant depression. Biol. Psychiatry 40, 151-153.

Inoue, T., Izumi, T., Koyama, T., 2002. Strategy of augmentation therapy for refractory depression. In: Okuma, T., Inoue, Y., Kanba, S. (Eds.), Recent Advances in the

Research of Affective Disorders in Japan, Elsevier Science, Amsterdam, pp. 147-151.

Janicak, P.G., Davis, J.M., Preskorn, S.H., 2002. Principles and Practice of Psychopharmacotherapy, 3rd ed. Lippincott Williams & Wilkins, Philadelphia.

Kraepelin, E., 1913. Psychiatrie. Ein Lehrbuch für Stuierende and Ärzte, achten Auflage. Johann Amrosius Barth, Leipzig.

Lam, R.W., Wan, D.D., Cohen, N.L., Kennedy, S.H., 2002. Combining antidepressants for treatment-resistant depression: a review. J. Clin.. Psychiatry 63, 685-93.

Lecrubier, Y., 2002. How do you define remission? Acta Psychatr. Scand. 106(Suppl 415) 7-11.

Lenderking, W.R., Tennen, H., Nackley, J.F., Hale, M.S., Turner, R.R., Testa, M.A., 1999. The effects of venlafaxine on social activity level in depressed outpatients. J. Clin. Psychiatry 60, 157-163.

Möller, H.J., 1991. Therapieresistenz auf Antidepressiva: Riskfaktoren und Behandlungsmoglichkeiten. Nervenarzt 62, 658-669.

National Institute of Mental Health, 1985. Specific feature: Rating scales and assessment instruments for use in pediatric pharmacology research. Psychopharmacol. Bull. 21(4).

Roose, S.P., Glassman, A.H., Walsh, B.T., Woodring, S., 1986. Tricyclic nonresponders: phenomenology and treatment. Am. J. Psychiatry 143, 345-8.

Roose, S.P., 1990. Methodological issues in the diagnosis, treatment, and study of refractory depression. In: Roose, S.P., Glassman, A.H. (Eds.), Treatment Strategies for Refractory Depression. Washington, DC. American Psychiatric Press, pp. 3-9.

Sharma, V., Khan, M., Smith, A., 2005. A closer look at treatment resistant depression: is it due to a bipolar diathesis? J. Affect. Disord. 84, 251-257.

Stimpson, N., Agrawal, N., Lewis, G., 2002. Randomised controlled trials investigating pharmacological and psychological interventions for treatment-refractory depression: Systematic review. Br. J. Psychiatry 181, 284-294.

Thase, M.E., Rush, A.J., 1995. Treatment-resistant depression. In: Bloom, F.E., Kupfer, D.J. (Eds.), Psychopharmacology: The Fourth Generation of Progress. Raven Press, New York, pp. 1081-1097.

Weitbrecht, H.J., 1973. Psychiatrie im Grundriss, dritte Auflage. Springer-Verlag, Berlin-Heidelberg-New York.

Table 1A. Summary of diagnoses and final outcomes for bipolar patients with refractory depression in the present study.

No.	Age	Sex	1995 Dx	Final Dx	Follow-up (years)	Final GAF	Severity in 1995	Final Severity	Social Functioning
1	25	M	BPD(I)	BPD(I)	5	30	Mild	Severe	Inpatient
2	66	M	BPD(I)	BPD(I)	7	25	Remission	Severe	Inpatient
3	51	M	BPD(II)	BPD(II)	7	70	Remission	Mild	Laid off
4	37	M	BPD(II)	BPD(II)	7	100	Mild	Remission	Work
5	53	M	BPD(II)	BPD(II)	7	90	Mild	Remission	Living at Home
6	43	F	MD(S)	BPD(I)	7	100	Mild	Remission	Work
7	51	F	MD(S)	BPD(II)	6	90	Mild	Remission	Living at Home
8	33	F	MD(S)	BPD(II)	7	65	Moderate	Mild	Housewife
9	51	M	MD(S)	BPD(II)	7	60	Moderate	Moderate	Living at Home
10	56	M	MD(R)	BPD(II)	7	90	Mild	Remission	Work

M, male; F, female; Dx, diagnosis; BPD(I), bipolar disorder I; BPD(II), bipolar disorder II, MD(S), major depression, single episode; MD(R), major depression, recurrent. Age, Final Dx, Final Severity and Social Function were evaluated at the final follow-up visit. Remission denotes full remission.

Table 1B. Summary of diagnoses and final outcomes among unipolar patients with refractory depression in the present study.

No.	Age	Sex	1995 Dx	Final Dx	Follow-up (years)	Final GAF	Severity in 1995	Final Severity	Social Functioning
1	55	M	MD(S)	MD(S)	7	70	Mild	Mild	Living at Home
2	36	M	MD(S)	MD(S)	1	70	Mild	Mild	Work
3	73	F	MD(S)	MD(S)	7	70	Moderate	Mild	Housewife
4	38	F	MD(S)	MD(S)	7	70	Moderate	Mild	Work
5	69	F	MD(S)	MD(S)	7	60	Mild	Moderate	Living at Home
6	59	F	MD(S)	MD(S)	2	80	Mild	Remission	Housewife
7	76	F	MD(S)	MD(S)	7	90	Moderate	Remission	Living at Home
8	66	M	MD(S)	MD(S)	2	90	Remission	Remission	Living at Home
9	29	F	MD(S)	MD(S)	3	90	Mild	Remission	Housewife
10	43	M	MD(S)	MD(S)	4	90	Mild	Remission	Work
11	62	F	MD(R)	MD(R)	7	70	Mild	Mild	Housewife
12	43	F	MD(R)	MD(R)	7	70	Mild	Mild	Housewife
13	66	F	MD(R)	MD(R)	7	50	Remission	Moderate	Living at Home
14	54	F	MD(R)	MD(R)	3	90	Remission	Remission	Housewife
15	69	F	MD(R)	MD(R)	2	90	Remission	Remission	Living at Home
16	38	M	MD(S)	MD(R)	7	100	Remission	Remission	Work

M, male; F, female; Dx, diagnosis; MD(S), major depression, single episode; MD(R), major depression, recurrent. Age, Final Dx, Final Severity and Social Function were evaluated at the final follow-up visit. Remission denotes full remission.

Table 2A. Summary of recurrence, remission, and effective augmentation treatments among bipolar patients with refractory depression in the present study.

No.	Recurrence after 1995	Remission after 1995	Effective Augmentation
1	1M, 1D	Yes	Pergolide
2	1M, 1D	Yes	Li, T4
3	3D	Yes	Bromocriptine, T4
4		Yes	Bromocriptine
5		Yes	Bromocriptine
6	1M, 1D	Yes	
7	1hM	Yes	Li, Pergolide
8	1hM	No	
9	1hM	No	
10	1hM, 1D	Yes	Li, T4

M, manic episode; hM, hypomanic episode; D, depressive episode (Number indicates the number of episodes). Remission denotes full remission. Effective augmentation therapies are indicated when full remission was achieved. T4, L-Thyroxine; Li, Lithium carbonate.

Table 2B. Summary of recurrence, remission, and effective augmentation treatments among unipolar patients with refractory depression in the present study.

No.	Recurrence after 1995	Remission after 1995	Effective Augmentation
1		No	
2		No	
3		No	
4		No	
5		No	
6		Yes	Li, T4
7		Yes	Bromocriptine
8		Yes	Bromocriptine
9		Yes	Bromocriptine
10		Yes	Bromocriptine
11		No	
12		No	
13	2D	Yes	Bromocriptine
14		Yes	Bromocriptine
15		Yes	Pergolide
16	1D	Yes	Bromocriptine

D, depressive episode (Number indicates the number of episodes). Remission denotes full remission.
Effective augmentation therapies are denoted when a full remission was achieved.
T4, L-Thyroxine; Li, Lithium carbonate.