revised to **Neuropsychopharmacology**

Treatment response in depressed patients with enhanced Ca mobilization stimulated by serotonin

Ichiro Kusumi, M.D., Ph.D., Katsuji Suzuki, M.D., Yuki Sasaki, B.Sc., Kensuke Kameda, M.D.,Ph.D., and Tsukasa Koyama, M.D., Ph.D.

Department of Psychiatry, Hokkaido University School of Medicine

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

Running title: Treatment response and Ca mobilization

Correspondence: Ichiro Kusumi, M.D., Ph.D.

TEL: +81-11-716-1161 ext.5973

FAX: +81-11-736-0956

e-mail: ikusumi@med.hokudai.ac.jp

ABSTRACTS

Serotonin (5-HT)-stimulated intraplatelet calcium (Ca) mobilization has been shown to be enhanced in nonmedicated depressive patients by many studies. However, there has not been any longitudinal follow-up study of this parameter. We examined the relationship between treatment response and pretreatment value of the 5-HT-induced Ca response. The 5-HT(10 uM)-induced intraplatelet Ca mobilization was measured in 98 nonmedicated depressive patients (24 bipolar disorders, 51 melancholic major depressive disorder and 23 non-melancholic major depressive disorder). These patients were followed up prospectively for a further period of 5 years. The depressed patients with enhanced Ca response to 5-HT in bipolar disorders exhibited a good response to mood stabilizers but those in major depressive disorders showed a poor response to antidepressants. These findings suggest the possibility that the 5-HT-induced intraplatelet Ca response may be a good predictor of treatment response in depressed patients. Longer longitudinal

follow-up studies are needed in larger samples to examine that this parameter may be a specific biological marker for unipolar-bipolar dichotomy.

KEY WORDS: Calcium, Serotonin, mood disorder, treatment response, Platelet

A large number of studies have indicated that central serotonin-2A (5-HT$_{2A}$) receptor dysfunction is an important factor in the etiology of mood disorders. Increased densities of 5-HT$_{2A}$ receptor binding sites in the postmortem brain of depressed patients or suicide victims, and platelets of depressed patients have been reported by many investigators (see review, Kusumi and Koyama 1998). An neuroendocrine study also suggested the supersensitivity of 5-HT$_{2A}$ receptors by showing that cortisol response to oral D, L-5-hydroxytryptophan was enhanced in nonmedicated depressed and manic patients (Meltzer et al. 1984). By measuring 5-HT-induced intraplatelet calcium (Ca) mobilization, we have already indicated that 5-HT$_{2A}$ receptor function is enhanced in nonmedicated patients with bipolar disorders and melancholic major depression compared to normal controls (Kusumi et al.

1991b, 1994). Although these findings were confirmed by several studies (Mikuni et al. 1992; Eckert et al. 1993; Okamoto et al. 1994; Konopka et al. 1996; Tomiyoshi et al. 1999), there has not been any follow-up study of this parameter except our previous report (Kusumi et al. 1994), which suggested that the enhanced Ca response is not state dependent, but trait dependent. Assuming that this parameter might be some predictor of treatment response in depressed patients, in this study, we examined the relationship between clinical improvement and pretreatment value of the 5-HT-induced intraplatelet Ca response in patients with bipolar disorders and major depressive disorders.

SUBJECTS AND METHODS

Subjects

The study reports on a total of 98 drug-free, major depressive patients and 30 normal controls. After complete description of the study, written informed consent was obtained from all participants. The depressed patients were diagnosed and subtyped using DSM-IV criteria, which consisited of 24 bipolar disorders, 51 major depressive disorders with melancholic feature and 23 major depressive disorders without melancholic feature. For at least 4 weeks before blood sampling they had not received any psychotropic medication or

any other drugs such as aspirin that might interfere with platelet aggregation. They were all free of physical illness including hypertension. The severity of depressive symptoms was assessed by the 17-item Hamilton Rating Scale for Depression (HRSD) at the time of sampling. Family history was investigated whether there was any patient with mood disorders within a first- or second-degree relative or not. The clinical data for subgroups of nonmedicated patients and normal controls are shown in Table 1.

Treatment response

All patients were observed their course of treatment at least monthly for a period of five years after blood sampling. Medications at follow-up were prescribed based on clinical judgment rather than by random assignment to a particular medication protocol. Responders were defined as patients with absence of DSM-IV (hypo)manic or major depressive episodes during at least 2 years of effective treatment despite a reasonably high risk of recurrence (history of at least one affective episode during the 1 year preceding the current episode) for bipolar disorders, and as a reduction to 5 or less of total HRSD score for major depressive disorders. On the other hand, non-responders were patients who experienced at least one affective episode for a

period of less than 2 years with onset after trials of various combination with adequate dose of mood stabilizers for bipolar disorders, and those who did not respond to an adequate period (more than 4 weeks) of treatment with at least two different antidepressants at optimal dosage (a minimum of the equivalent of 150mg imipramine per day) for major depressive disorders.

5-HT-stimulated Ca response

The isolation of platelets and the measurement of intraplatelet Ca concentration were performed as described previously (Kusumi et al. 1991a; 1994). Briefly, platelet-rich plasma was incubated with 4 uM fura-2/acetoxymethylester, a Ca sensitive fluorescent probe, for 15 min at 37^{o}C. After centrifugation, the resulting platelet pellet was suspended at 1 X 10^{8} cells/ml in Krebs-Ringer HEPES buffer. The samples were prewarmed in a cuvette at 37^{o}C for 4 min and then 10 uM 5-HT was added to the incubation medium. Fluorescence was measured on a Hitachi F-2000 fluorometer with excitation at 340 and 380 nm, and with emission at 510 nm. Intracellular Ca concentrations were calculated from the ratio of fluorescence intensities at two excitation wavelengths in the platelet samples according to the method of Grynkiewicz et al. (1985). We examined both resting Ca concentration and

maximum Ca response (% increase = initial peak (nM) / resting level (nM) X 100) induced by 10uM of 5-HT. Since data expressed by % increase is more stable (lower inter- or intra-assay) than those by Ca increase (initial peak minus resting Ca level) as suggested in the previous report (Kusumi et al. 1991a), we analysed data with % increase in this longitudinal follow-up study.

Statisitical analysis

Results are expressed as means ± SD. Statisitical analysis was performed using Student's t-test, Mann-Whittney's U test, or one-way analysis of variance (ANOVA) for multiple comparison followed by Scheffe's test. Analysis by É‘² was used to assess the relationship between pretreatment Ca mobilization and clinical response. P values less than 0.05 were considered statistically significant.

RESULTS

Clinical characteristics of depressive patients

Comparing the demographic data for subgroups of nonmedicated depressive patients, there were no significant differences in sex ratio, age, family history or total HRSD score among three groups (Table 1). The maximal Ca response

induced by 10 uM 5-HT was significantly higher in patients with bipolar disorders than in normal controls, while no significant difference in basal Ca concentration was observed among four groups (Table 1). We did not find any difference in both basal Ca level and 5-HT-stimulated Ca response between male and female when examining for total or each subgroup of depressed patients (data not shown). Thus, further analyses were performed with male and female patients together. No significant correlation was observed between total HRSD score and the 5-HT-induced Ca mobilization in the entire group or each subgroup of patients (data not shown).

Treatment response in depressed patients

First, we examined clinical characteristics and the 5-HT-stimulated Ca mobilization for responder and nonresponder in our present sample. In bipolar disorders, although there were no significant differences in age, family history or total HRSD score between responder and nonresponder, the 5-HT-induced Ca mobilization in responder was significantly higher than in nonresponder (Table 2). Basal Ca level in responder was significantly lower than in nonresponder. On the other hand, in melancholic major depressive disorder, the 5-HT-stimulated Ca mobilization in responder was significantly lower than

in nonresponder (Table 3). No significant differences were observed in age, family history, total HRSD score or basal Ca concentration between both groups (Table 3). In nonmelancholic major depressive disorder, there were no significant differences in the 5-HT-induced Ca response, basal Ca level or other clinical index between responder and nonresponder (Table 4).

Characteristics of depressive patients with enhanced Ca response

To examine the role of increased Ca response, we classified the patients as "enhanced" and "the others" groups according to their pretreatment value of the 5-HT-induced Ca response. The cut-off value chosen was 280% of basal, since it corresponded to the value of the mean + 2SD for normal controls (Table 1). The number of patients with a Ca response higher than this value was 24 (24.5% of total), of whom 10 (40%) were bipolar disorders, 13 (26%) were melancholic major depressive disorders and only 1 (4%) was a non-melancholic major depressive disorder (Table 5). The demographic characteristics of nonmedicated depressive patients with a Ca response above 280% and below 280% are shown in Table 5. There were no significant differences in age, family history or total HRSD score between the two

groups. Basal Ca level in patients with a Ca response above 280% was significantly lower than in those below 280% (Table 5).

Next, we examined the treatment response for patients with a pretreatment Ca response above 280% and below 280%. The clinical response to mood stabilizers in the patients with bipolar disorders are shown in Table 6. Chi-squared analysis of the data revealed a significantly higher response rate in patients with a pretreatment Ca response above 280% than those below 280% (60% vs 7%, p=0.005, N=24). Final effective treatments were all lithium carbonate, of which 3 were coadministered with sodium valproate. There was no difference in medical approach between responders and non-responders because all patients were treated with one of mood stabilizers (firstly lithium carbonate and secondly sodium valproate or carbamazepine), then in case of no efficacy, the various combinations of these agents. The clinical response to antidepressants in the patients with major depressive disorders are also shown in Table 6. In contrast with the result for bipolar disorders, patients with a Ca response above 280% showed a significantly lower response rate than those below 280% (14% vs 58%, p=0.003 for total patients, N=74; 15% vs 61%, p=0.005 for melancholic major depressive disorder, N=51; 0% vs 55%, p=0.48 for non-melancholic major depressive

disorder, Fisher's exact method, N=23). 5-HT$_{2A}$ receptor antagonists, amoxapine (46% of responder) or setiptiline (11%) appeared to be effective for major depressive patients with a Ca response below 280% (Table 6). There was no difference in medical approach between responders and non-responders because most patients were firstly treated with amoxapine or clomipramine, secondly imipramine, sulpiride or tetracyclic antidepressants, then in case of no efficacy, bromocriptine or novel selective 5-HT and/or noradrenaline reuptake inhibitor

DISCUSSION

The present results indicate that depressed patients with enhanced Ca response to 5-HT in bipolar disorders exhibit a good response to mood stabilizers but that those in major depressive disorders show a poor response to antidepressants. These findings suggest the possibility that the 5-HT-induced intraplatelet Ca mobilization may be a good predictor of treatment response in depressed patients. Many investigators have confirmed our previous finding that the 5-HT-induced Ca response is enhanced in some types of mood disorders as mentioned in the introduction, but there has not been any longitudinal follow-up study of this parameter except our previous report

(Kusumi et al. 1994), which showed that the enhanced Ca response to 5-HT is not normalized after the remission of depressive symptoms. This is the first follow-up study examining the relationship between treatment response and pretreatment 5-HT-induced Ca mobilization in both patients with bipolar disorders and major depressive disorders.

As shown in our previous report (Kusumi et al. 1991a), the 5-HT-stimulated intraplatelet Ca mobilization is a stable marker since it is not significantly affected by sampling time and season, sex, age, meal or exercise in healthy subjects. This study showed that sex and age did not significantly influence this parameter in depressed patient sample. The 5-HT-induced Ca mobilization in responder was significantly different from that in nonresponder for patients with bipolar disorders and melancholic major depressive disorder although there were no significant differences in clinical characteristics such as the severity of depressive symptoms and the family history. In bipolar disorders, responder to mood stabilizers exhibited a significant higher Ca response to 5-HT than nonresponder, while responder to antidepressants showed a significant lower Ca response than nonresponder in melancholic major depressive disorder. In nonmelancholic major depressive disorder, no significant difference was found in the 5-HT-stimulated Ca

mobilization between responder and nonresponder. Moreover, comparing enhanced Ca response group which showed more than 280% of basal with the other one, similar results were obtained for both bipolar disorders and melancholic major depressive disorder. In bipolar disorders, the group with enhanced Ca mobilization demonstrated a significantly higher response to mood stabilizers than the other one. In melancholic major depressive disorder, however, the former exhibited a significantly lower response to antidepressants than the latter. These findings indirectly suggest that bipolar disorder and major depressive disorder may be due to the different pathophysiology even if a part of patients in both disorders show enhanced Ca response to 5-HT. In fact, ratio of patients with enhanced Ca response was different among the three subgroups of depressive patients. Bipolar disorder was most frequent (40%), followed by melancholic major depressive disorder (26%) and nonmelancholic major depressive disorder (4%). Moreover, in contrast with our previous report (Kusumi et al. 1994), in the present study using a larger sample, the 5-HT-stimulated Ca response in melancholic major depressive disorder was not significantly different from that in normal control (Table 1). Therefore, it is possible that the enhanced Ca response may be a specific marker for bipolar disorders. In the previous study, a group of

melancholic major depression could include potential bipolar patients, which might influence the results. Indeed, during the follow-up observation, the diagnosis was changed from major depressive disorder to bipolar disorder in two patients with enhanced Ca response. In this sense, the diagnosis of monopolar depression may be changeable, thus longer longitudinal follow-up study is necessary in a larger sample in future.

It is interesting to note the final effective treatments for responder in our sample. In bipolar disorders, all responders exhibited a good response to lithium carbonate. On the other hand, in melancholic major depressive disorder, 13 of 23 responders (57%) in the patients with a pretreatment Ca response below 280% showed a good response to 5-HT_{2A} receptor antagonist amoxapine. In nonmelancholic major depressive disorder, 7 of 12 responders (58%) in the patients with a Ca response below 280% indicated a good response to 5-HT_{2A} receptor antagonist setiptiline or amoxapine. We have expected that patients with an enhanced Ca response to 5-HT exhibited a good response to 5-HT_{2A} receptor antagonist, thus this result is completely reverse. There may be several possible reasons for this unexpected finding. First, the cut-off value for the enhanced Ca response (280%) was so high that clinical dose of 5-HT_{2A} receptor antagonist failed to inhibit the 5-HT-induced Ca

response. However, this possibility is not plausible because inhibition of Ca mobilization is not necessarily correlated with treatment response in our preliminary study. Second, the enhanced Ca response observed in depressed patients may not be specifically mediated by 5-HT_{2A} receptor. It has been previously reported that thrombin-stimulated Ca response was enhanced in nonmedicated depressive patients with bipolar disorders compared to those with major depression and normal control (Dubovsky et al. 1991; Kusumi et al. 1992). In bipolar disorders, there might be some alterations in intracellular signal transduction that are common to both 5-HT- and thrombin-induced Ca mobilizing pathways. This possibility is partly supported by the reports that hyperfunction of GTP binding protein is observed in the leukocytes of bipolar patients (Schreiber et al. 1991; Young et al. 1994). Agonist-stimulated Ca response in neutrophils from patients with bipolar disorders was also enhanced, which was significantly attenuated by lithium treatment (Foerstner et al. 1994). These findings may suggest that bipolar disorders are associated with a nonspecific hypersensitivity of the inositol phospholipid second-messenger generating system. As mentioned above, if enhanced Ca response might be a specific marker for bipolar disorders, it does not necessarily conflict with the results that the patients with enhanced Ca mobilization

exhibited a good response to mood stabilizers and a poor response to antidepressants including 5-HT$_{2A}$ receptor antagonists.

As for the basal Ca concentration, most reserchers except Dubovsky et al.(1991) and Konopka et al.(1996) have shown that there is no significant difference between depressed patients and normal controls (Kusumi et al. 1991b; 1994; Mikuni et al. 1992; Eckert et al. 1993; Okamoto et al. 1994; Bothwell et al. 1994; Tomoyoshi et al. 1999). In this study, this finding was reconfirmed when comparing by DSM-IV subtype (Table 1). However, responders in bipolar disorder had lower resting Ca level than non-responders (Table 2) although no significant differences were observed in major depressive disorder with and without melancholic features (Table 3 and 4). Moreover, basal Ca level in patients with a Ca response above 280% was significantly lower than in those below 280% (Table 5). It is not plausible that higher 5-HT-induced Ca response may be due to lower basal Ca concentration since the same findings were observed when examining by absolute Ca increase (initial peak minus resting Ca level) instead of % increase. The reason for lower basal Ca level in bipolar responder is unknown from the present study. However, it is not possible that the basal Ca concentration can predict the Ca responsiveness to 5-HT because there was no significant correlation

between the resting Ca level and 5-HT-induced Ca increase in patients with bipolar disorder (N=24, r=0.31, p=0.13, Pearson's correlation coefficient). Cosidering the report of Tan et al.(1990) that the basal Ca concentration was higher in lithium-treated euthymic bipolar patients than in controls, the possibility exists that effective lithium treatment may elevate basal Ca level by affecting the mechanism for maintaining intracellular Ca level such as Ca pump, Ca storing and forming complexes of Ca with intracellular proteins and phospholipids. Therefore, it seems to be a good possibility that low resting Ca level may predict a good responsiveness to mood stabilizers for bipolar disorder, which should be reconfirmed in further studies.

In conclusion, the depressed patients with enhanced Ca mobilization exhibited a good response to mood stabilizers but those in major depressive disorders show a poor response to antidepressants. These findings suggest the possibility that the 5-HT-induced intraplatelet Ca response may be a good predictor of treatment response in depressed patients. In future, longer longitudinal follow-up studies are needed in larger samples to examine that this parameter may be a specific biological marker for unipolar-bipolar dichotomy.

ACKNOWLEDGMENTS

This work was partly supported by grants from the Akiyama Foundation, the Japanese Research Foundation for Clinical Pharmacology and the Pharmacopsychiatry Research Foundation.

REFERENCES

Dubovsky SL, Lee C, Christiano J, Murphy J (1991): Elevated platelet intracellular calcium concentration in bipolar depression. Biol Psychiatry 29: 441-450.

Eckert A, Riemann GD, Aldenhoff J, Mueller WE (1993): Elevated intracellular calcium levels after 5-HT_2 receptor stimulation in platelets of depressed patients. Biol Psychiatry 34: 565-568.

Foerstner U, Bohus M, Gebicke-Haerter PJ, Baumer B, Berger M, van Calker D (1994): Decreased agonist-stimulated Ca^{2+} response in neutrophils from patients under chronic lithium therapy. Eur Arch Psychiatry Clin Neurosci 243: 240-243.

Grynkiewicz G, Poenie M, Tsien RY (1985): A new generation of Ca^{2+} indicators with greatly improved fluorescence properties. J Biol Chem 260: 3440-3450.

Konopka LM, Cooper R, Crayton JW (1996): Serotonin-induced increases in platelet cytosolic calcium concentration in depressed, schizophrenic, and substance abuse patients. Biol Psychiatry 39: 708-713.

Kusumi I, Koyama T, Yamashita I (1991a): Effect of various factors on serotonin-induced Ca^{2+} response in human platelets. Life Sci 48: 2405-2412.

Kusumi I, Koyama T, Yamashita I (1991b): Serotonin-stimulated Ca^{2+} response is increased in the platelets of depressed patients. Biol Psychiatry 30: 310-312.

Kusumi I, Koyama T, Yamashita I (1992): Thromibn-induced platelet calcium mobilization is enhanced in bipolar disorder. Biol Psychiatry 32: 731-734.

Kusumi I, Koyama T, Yamashita I (1994): Serotonin-induced platelet intracellular calcium mobilization in depressed patients. Psychopharmacology 113: 322-327.

Kusumi I, Koyama T (1998): Serotonin-2A receptor function in affective disorders. In: Ozawa H, Saito T, Takahata N, editors. Signal Transduction in Affective Disorders. Tokyo: Springer, pp21-34.

Meltzer HY, Umberkoman-Wiita B, Robertson A, Tricou BJ, Lowy M, Perline R (1984): Effect of 5-hydroxytryptophan on serum cortisol levels in major affective disorders; I. Enhanced response in depression and mania. Arch Gen Psychiatry 41: 366-374.

Mikuni M, Kagaya A, Takahashi K, Meltzer HY (1992): Serotonin but not norepinephrine-induced calcium mobilization of platelets in enhanced in affective disorders. Psychopharmacology 106: 311-314.

Okamoto Y, Kagaya A, Shinno H, Motohashi N, Yamawaki S (1994): Serotonin-induced platelet calcium mobilization is enhanced in mania. Life Sci 56: 327-332.

Schreiber G, Avissar S, Danon A, Belmaker RH (1991): Hyperfunctional G proteins in mononuclear leukocytes of patients with mania. Biol Psychiatry 29: 273-280.

Tan CH, Javors MA, Seleshi E, Lowrimore PA, Bowden CL (1990): Effects of lithium on platelet ionic intracellular calcium concentration in patients with bipolar (manic-depressive) disorder and healthy controls. Life Sci 46: 1175-1180.

Tomiyoshi R, Kamei K, Muraoka S, Muneoka K, Takigawa M (1999): Serotonin-induced platelet intracellular Ca^{2+} responses in untreated depressed patients and imipramine responders in remission. Biol Psychiatry 45: 1042-1048.

Young LT, Li PP, Kamble A, Siu KP, Warsh JJ (1994): Mononuclear

leukocyte levels of G proteins with bipolar disorder or major depressive disorder. Am J Psychiatry 151: 594-596.

Table 1. Clinical Data for Subgroups of Nonmedicated Depressive Patients and normal controls

	Bipolar disorders	Major depressive disorder with melancholc features	Major depressive disorder without melancholic features	Controls
N	24	51	23	30
Male/Female	10/14	21/30	12/11	14/16
Age (year)	36.8±14.6	42.1±16.3	39.1±15.2	42.8±11.0
Family history *a	4 (17%)	9 (18%)	5 (22%)	
HRSD *b	21.3±6.1	23.4±7.6	20.3±5.6	
Resting Ca level (nM)	68.5±17.3	69.1±15.9	69.9±20.9	76.2±13.1
5-HT-induced Ca response (%)	272.1±58.3**	247.6±50.5	221.9±32.7	225.5±27.8

*a Family history of mood disorders in a first- or second degree relative

*b Hamilton Rating Scale for Depression

** $p<0.005$ vs. Controls

Table 2. Response to Mood Stabilizers in Patients with Bipolar Disorders

	Responder	Nonresponder	t-test *c
N	7	17	
Male/Female	2/5	8/9	N.S.
Age (year)	40.9±18.4	35.2±12.9	N.S.
Family history *a	1 (14%)	3 (18%)	N.S.
HRSD *b	23.8±3.7	20.5±6.6	N.S.
Resting Ca level (nM)	56.8±13.2	73.3±16.8	$p<0.05$
5-HT-induced Ca response (%)	331.4±51.2	247.8±41.7	$p<0.0005$

*a Family history of mood disorders in a first- or second degree relative

*b Hamilton Rating Scale for Depression

*c N.S.: not significant

Table 3. Response to Antidepressants in Patients with Melancholic Major Depressive Disorder

	Responder	Nonresponder	t-test *c
N	25	26	
Male/Female	11/14	10/16	N.S.
Age (year)	41.0±16.3	43.1±16.6	N.S.
Family history *a	4 (16%)	5 (19%)	N.S.
HRSD *b	23.5±7.5	23.3±7.8	N.S.
Resting Ca level (nM)	69.3±16.4	68.9±15.8	N.S.
5-HT-induced Ca response (%)	226.6±35.2	267.9±55.1	$p<0.005$*d

*a Family history of mood disorders in a first- or second degree relative

*b Hamilton Rating Scale for Depression

*c N.S.: not significant

*d Mann-Whittney's U test

Table 4. Response to Antidepressants in Patients with Nonmelancholic Major Depressive Disorder

	Responder	Nonresponder	t-test *c
N	12	11	
Male/Female	7/5	5/6	N.S.
Age (year)	36.1±15.6	42.5±14.9	N.S.
Family history *a	4 (33%)	1 (9%)	N.S.
HRSD *b	21.8±4.6	18.6±6.2	N.S.
Resting Ca level (nM)	73.3±16.7	66.2±24.9	N.S.
5-HT-induced Ca response (%)	225.9±27.9	217.6±38.2	N.S.

*a Family history of mood disorders in a first- or second degree relative

*b Hamilton Rating Scale for Depression

*c N.S.: not significant

Table 5. Characteristics of Nonmedicated Depressive Patients with Enhanced Ca Response

	Ca response > 280%	Ca response < 280%	t-test *c
N	24	74	
Male/Female	12/12	31/43	N.S.
Age (year)	42.3±16.2	39.4±15.5	N.S.
Family history *a	5 (21%)	13 (18%)	N.S.
HRSD *b	23.7±5.7	21.6±7.1	N.S.
Resting Ca level (nM)	60.8±17.6	71.2±17.1	$p<0.01$
5-HT-induced Ca response (%)	318.0±35.3	224.8±31.6	
Bipolar disorder	10 (40%)	14 (60%)	
Melancholic major depressive disorder	13 (26%)	38 (74%)	
Nonmelancholic major depressive disorder	1 (4%)	22 (96%)	

*a Family history of mood disorders in a first- or second degree relative

*b Hamilton Rating Scale for Depression

*c N.S.: not significant

Table 6. Ratio of Patients with a Good Treatment Response for Bipolar Disorder and Major Depressive Disorders

Patient group	N	Good treatment response	Effective treatments
Bipolar disorder			
Ca response > 280%	10	6 (60%)	Li 4, Li/VPA 2
Ca response < 280%	14	1 (7%)	Li/VPA 1
Major depressive disorder with melancholic features			
Ca response > 280%	13	2 (15%)	BRM 2
Ca response < 280%	38	23 (61%)	AMX 11, AMX/BRM 2, IMI 3, CMI 2 IMI/TRZ 1, TRZ 1, MNP 1, MCI 1, DLX 1
Major depressive disorder without melancholic feature			
Ca response > 280%	1	0 (0%)	
Ca response < 280%	22	12 (55%)	STP 4, AMX 3, MPL 2 CMI 1, MIA 1, SUL 1

AMX: amoxapine, BRM: bromocriptine, CMI: clomipramine, DLX: duloxetine, IMI: imipramine, Li: lithium carbonate, MCI: MCI-225 (selective noradrenaline reuptake inhibitor), MIA: mianserin, MNP: milnacipran, MPL: maprotiline, STP: setiptiline, SUL: sulpiride, TRZ: trazodone, VPA: sodium valproate