BRIEF REPORT
https://doi.org/10.30773/pi.2022.0160
Print ISSN 1738-3684 / On-line ISSN 1976-3026
OPEN ACCESS

Prediction of 12-Week Remission by Psychopharmacological Treatment Step in Patients With Depressive Disorders

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Objective To investigate the predictors of remission by 4 treatment steps in depressive outpatients receiving 12-week psychopharmacotherapy.

Methods Patients were consecutively recruited at a university hospital in South Korea from March 2012 to April 2017. At baseline, 1,262 patients were evaluated for sociodemographic and clinical data including assessments scales, and were received antidepressant monotherapy. For patients with an insufficient response or uncomfortable side effects, next treatment steps (1, 2, 3, and 4) with alternative strategies (switching, augmentation, combination, and mixtures of these approaches) were administered considering measurements and patient preference at every 3 weeks in the acute treatment phase (3, 6, 9, and 12 weeks). Remission was defined as a Hamilton Depression Rating Scale score of ≤7.

Results In the multi-variate logistic regression analyses, remission was predicted by higher functional levels in patients received Step 1 and 2 treatment; by lower life stressors in Step 1; by higher social support in Step 3 and 4; and by lower suicidality in Step 1–3.

Conclusion Differential associations were found between symptoms or functions and treatment steps, which suggested that multi-faceted evaluations at baseline could predict remission by treatment steps. Psychiatry Investig 2022;19(10):866-871

Keywords Depression; Remission; Prediction; Pharmacotherapy; Treatment step.

INTRODUCTION

Depression is common and causes significant disability. Achieving remission, defined as low or absent symptom levels, has been considered as the treatment goal. However, remission rates were less than one third of cases in 8- to 12-week antidepressant trials.[1,2] Identifying subpopulations who are likely to experience better treatment responses is a practical option for increasing remission probabilities. A variety of socioeconomic and clinical factors represent the typical predictors of depression treatment outcomes.[1,2] These results have usually been drawn from trials with only a few antidepressants for the entire treatment period. However, there is accumulating evidence suggesting that antidepressant responses can be found within 2−3 weeks after treatment,[3] and therefore earlier clinical decision for changing pharmacological regime may enhance treatment outcomes.[4,5] Relevant to these hypotheses, we recently reported the predictors of remission in over four step psychopharmacotherapy based on early clinical decision.[6] Determining predictors of remission would be beneficial for personalized treatment, nonetheless it has not been investigated so far. Thus, we aimed to investigate the predictors of remission in each treatment step in 12-week psychopharmacotherapy in patients with depressive disorders.

Received: June 10, 2022 **Revised:** August 4, 2022
Accepted: August 22, 2022

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METHODS

Study outline

This was a secondary analysis, carried out as a component of the MAKE Biomarker discovery for Enhancing anTidepressant Treatment Effect and Response (MAKE BETTER) project, which intends to develop a treatment-response prediction index composed of bio-psycho-social markers for patients with depressive disorders. Study details have been published as a protocol paper[7] and registered with cris.nih.go.kr (identifier: KCT0001332). To reflect real-world settings, participants enrolment and treatment interventions were con-

ducted in a naturalistic fashion. This study was approved by the Chonnam National University Hospital Institutional Review Board (CNUH 2012-014).

Participants

Patients with depressive disorders who fulfilled the eligibility criteria (Supplementary Material 1 in the online-only Data Supplement) were consecutively recruited from March 2012 to April 2017 from those who had visited the outpatient psychiatric department of CNUH. All inclusion instances represented new treatment episodes—i.e., taking newly initiated antidepressant treatment—whether depressive symptoms were first-onset or recurrent. All participants reviewed the consent form and written informed consent was obtained.

Baseline evaluations

Socio-demographic characteristics obtained comprised age, sex, year of formal education, marital status, cohabiting status, religion, occupation, and monthly income. Clinical characteristics evaluated comprised diagnoses of major depressive disorder or others with certain specifiers based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria,[8] age at onset and duration of illnesses, history of previous depressive episodes, number of previous depressive episodes, duration of present episode, family history of depression, and number of concurrent physical disorders (applying a questionnaire enquiring about 15 different systems or disorders). Although the DSM-5 criteria were updated in 2013,[9] the enrollment was conducted from 2012 to 2017 and then, DSM-IV version of depressive disorder instead of DSM-5 should be used as a standard. Assessment scales for investigating symptoms and function were administered. Depressive symptoms were assessed using the Hamilton Depression Rating Scale (HAMD);[10] anxiety symptoms by the Hospital Anxiety and Depression Scale-anxiety subscale (HADS-A);[11] quality of life by the EuroQol-5D (EQ-5D);[12] functioning levels by the Social and Occupational Functioning Assessment Scale (SOFAS);[8] number of stressful life events by the Life Experiences Survey (LES);[13] subjective perception of stress by the Perceived Stress Scale (PSS);[14] psychological resilience by the Connor-Davidson Resilience Scale (CDRS);[15] social support deficits by the Multidimensional Scale of Perceived Social Support (MSPSS);[16] and suicide severity was assessed with the Brief Psychiatric Rating Scale (BPRS)[17] suicidality item. Higher scores on HAMD, HADS-A, LES, PSS, and BPRS suicidality item indicate more severe symptomatology, as do lower scores on EQ-5D, SOFAS, CDRS, and MSPSS.

Stepwise pharmacotherapy

Treatment steps and strategies were published previously[5] and described in detail (Supplementary Material 1 and Supplementary Figure 1 in the online-only Data Supplement). In brief, before the treatment commencement, a comprehensive examination was conducted for patients' clinical manifestations, illness severity, physical comorbidities and medication lists, and history of prior treatments. In the first step, patients received antidepressant medication, considering these patient data and existing treatment guidelines for 3 weeks. General effectiveness and tolerability were evaluated for going ahead with every 3 weeks next-step measurement-based treatments. In cases of inadequate improvement or intolerable adverse events, patients were directed to choose whether they would prefer to stay in the present step or get in the next step treatment with switching antidepressants (S), augmenting with other drugs (A), combination of other antidepressants (C), S+A, S+C, A+C, and S+A+C strategies. Overall, up to 4 treatment step could be possible. For settling treatment strategies, patient's opinion was given priority.

Definition of remission

Remission status was assessed at every 3 weeks (at 3, 6, 9, and 12 weeks). Patients evaluated at least once after baseline comprised the analysed sample. At each assessment point, remission was defined as a HAMD score ≤7. Achievement of 12-week remission was defined only when these were maintained up to the 12-week assessment points.

Statistical analysis

Baseline data were compared between patients achieved remission and didn't by the four treatment steps (Step 1, 2, 3, and 4) using t-test or χ^2 test, as appropriate. Variables significantly associated with remission ($p<0.05$) were entered into a multiple logistic regression model to identify independent predictors. Statistical analyses were carried out using the SPSS 21.0 software (IBM Co., Armonk, NY, USA).

RESULTS

Recruitment and treatment flow

Patient flow by treatment strategies and steps in Supplementary Figure 1 (in the online-only Data Supplement). Of 1,262 patients evaluated at baseline, 1,246 (98.7%) were followed at least once during the 12-week treatment period and comprised the analyzed sample. Remission was achieved in 540 (43.3%) patients.

Uni-variate associations with remission by treatment steps

At the 12-week point, 534 (42.9%) patients received Step 1 antidepressant monotherapy treatment, 412 (33.1%) received

Table 1. Baseline characteristics by 12-week remission status according to treatment steps in 1,246 patients with depressive disorders

	Step 1 (N=534)		Step 2 (N=412)		Step 3 (N=226)		Step 4 (N=74)	
	No remission (N=347)	Remission (N=187)	No remission (N=217)	Remission (N=195)	No remission (N=109)	Remission (N=117)	No remission (N=33)	Remission (N=41)
Socio-demographic characteristics								
Age (yr)	56.0±15.3	60.1±13.0†	56.6±15.8	59.1±13.9*	53.2±17.1	56.9±14.6	50.2±16.8	51.6±14.6
Sex, female	253 (72.9)	131 (70.1)	148 (68.2)	132 (67.7)	74 (67.9)	71 (60.7)	22 (66.7)	31 (75.6)
Education (yr)	9.1±4.6	8.8±4.7	8.9±4.9	9.2±4.8	9.3±4.7	9.2±5.4	10.8±4.3	9.8±4.6
Marital status, married	234 (67.4)	133 (71.1)	141 (65.0)	146 (74.9)*	72 (66.1)	83 (70.9)	23 (69.7)	31 (75.6)
Living alone	56 (16.1)	32 (17.1)	31 (14.3)	28 (14.4)	19 (17.4)	16 (13.7)	2 (6.1)	3 (7.3)
Religious affiliation	159 (45.8)	73 (39.0)	97 (44.7)	83 (42.6)	43 (39.4)	51 (43.6)	19 (57.6)	20 (48.8)
Employed status	249 (71.8)	141 (75.4)	149 (68.7)	133 (68.2)	73 (67.0)	87 (74.4)	18 (54.5)	32 (78.0)*
Monthly income, <2,000 USD	218 (62.8)	116 (62.0)	132 (60.8)	107 (54.9)	67 (61.5)	65 (55.6)	17 (51.5)	18 (43.9)
Clinical characteristics								
Major depressive disorder	286 (82.4)	156 (83.4)	193 (88.9)	160 (82.1)	96 (88.1)	105 (89.7)	29 (87.9)	38 (92.7)
Melancholic feature	44 (12.7)	26 (13.9)	37 (17.1)	24 (12.3)	20 (18.3)	18 (15.4)	9 (27.3)	8 (19.5)
Atypical feature	13 (3.7)	5 (2.7)	15 (6.9)	13 (6.7)	15 (13.8)	7 (6.0)*	4 (12.1)	10 (24.4)
Age at onset (yr)	50.9±17.5	55.1±15.4†	51.7±16.9	55.3±15.5*	47.4±17.4	52.0±16.1*	45.6±18.5	46.3±15.9
Duration of illness (yr)	5.2±9.1	5.0±9.2	4.9±9.0	3.8±7.1	5.8±9.0	4.9±9.9	4.6±6.6	5.3±7.3
Recurrent depression	183 (52.7)	88 (47.1)	110 (50.7)	93 (47.7)	64 (58.7)	62 (53.0)	16 (48.5)	29 (70.7)
Number of depressive episodes	1.1±1.4	1.0±1.5	1.0±1.4	0.9±1.4	1.4±1.8	1.0±1.2*	1.9±2.6	1.4±1.3
Duration of present episode (mon)	7.8±11.0	6.3±7.6	8.1±12.8	6.5±8.1	8.5±11.5	6.3±8.1	11.2±15.7	6.6±10.4
Family history of depression	52 (15.0)	21 (11.2)	28 (12.9)	23 (11.8)	15 (13.8)	29 (24.8)*	5 (15.2)	10 (24.4)
Number of physical disorders	1.6±1.3	1.6±1.1	1.5±1.2	1.7±1.3	1.7±1.3	1.7±1.3	1.6±1.5	1.9±1.3
Assessment scales								
Hamilton Depression Rating Scale	20.7±4.1	20.2±4.4	21.4±4.6	20.2±3.9†	20.9±4.0	20.5±4.3	23.1±4.4	21.6±3.8
Hospital Anxiety and Depression Scale-anxiety subscale	11.6±4.1	10.6±3.9†	12.3±3.8	11.3±4.0†	12.5±4.1	12.2±4.2	13.9±3.6	12.5±4.2
EuroQol-5D	0.69±0.16	0.71±0.15	0.65±0.16	0.70±0.14†	0.66±0.15	0.67±0.17	0.64±0.17	0.64±0.15
Social and Occupational Functional Assessment Scale	55.8±7.4	57.9±7.6†	54.0±8.2	56.7±6.7‡	54.5±7.4	56.5±7.1*	52.9±8.2	57.2±7.6*
Life Experiences Survey	2.1±1.3	1.7±1.1†	2.0±1.5	1.9±2.0	2.3±1.8	2.1±1.6	3.7±4.4	2.2±2.5
Perceived Stress Scale	26.8±6.3	25.4±6.7*	27.7±6.6	26.8±6.5	28.6±6.8	27.9±5.2	29.0±6.9	26.9±7.0
Connor-Davidson Resilience Scale	44.0±17.3	47.9±17.8*	40.0±18.2	44.5±18.3*	38.5±18.0	42.6±16.4	35.9±19.2	39.0±17.7
Multidimensional Scale of Perceived Social Support	38.6±12.2	40.2±11.9	38.5±12.3	40.6±11.7	36.3±11.5	40.4±10.7†	38.3±12.3	42.8±10.6*
Brief Psychiatric Rating Scale suicidality item	2.9±1.3	2.4±1.2‡	3.1±1.4	2.5±1.4‡	3.3±1.4	2.9±1.4*	2.9±1.4	3.1±1.6

Values are presented as mean±standard deviation or number (%). The treatment steps were administered from antidepressant monotherapy (Step 1) to Step 4, every 3 weeks during 12 weeks considering overall effectiveness and tolerability. At the next step, Step 1 monotherapy continuation including dose adjustment or enter into Step 2, 3, and 4 composed of adding strategies of previous step with switching, augmentation, combination treatment. Antidepressants initiated, switched or combined were bupropion, desvenlafaxine, duloxetine, escitaloproam, fluoxetine, mirtazapine, paroxetine, sertraline, venlafaxine, and vortioxetine. Augmented drugs were buspiron, lithium, triiodothyronine, and atypical antipsychotics including aripirprazole, risperidone, olanzapine, quetiapine, and ziprasidone. Treatment strategies were continuing initial monotherapy (M), switching antidepressants (S), augmenting with other drugs (A), combination of other antidepressants (C), S+A, S+C, A+C, and S+A+C. *p<0.05; †p<0.01; ‡p<0.001

Table 2. Predictors of 12-week remission by treatment steps in 1,246 patients with depressive disorders

	Step 1 (N=534)		Step 2 (N=412)		Step 3 (N=226)		Step 4 (N=74)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, higher	1.02 (0.99–1.04)	0.182	1.00 (0.97–1.02)	0.740	-	-	-	-
Married marital state	-	-	1.33 (0.95–1.57)	0.083	-	-	-	-
Employed state	-	-	-	-	-	-	1.17 (0.73–1.85)	0.127
Atypical feature	-	-	-	-	0.51 (0.17–1.44)	0.196	-	-
Age at onset, higher	1.00 (0.98–1.02)	0.969	1.02 (0.99–1.04)	0.234	1.01 (0.99–1.03)	0.430	-	-
Number of depressive episodes, lower	-	-	-	-	1.09 (0.89–1.35)	0.341	-	-
Family history of depression	-	-	-	-	1.80 (0.87–3.74)	0.115	-	-
Hamilton Depression Rating Scale, lower	-	-	1.01 (0.94–1.08)	0.864	-	-	-	-
Hospital Anxiety & Depression Scale-anxiety subscale, lower	1.01 (0.94–1.08)	0.862	1.01 (0.93–1.11)	0.848	-	-	-	-
EuroQol-5D, higher	-	-	1.07 (0.91–1.26)	0.374	-	-	-	-
Social and Occupational Functional Assessment Scale, higher	1.03 (1.00–1.06)	0.048	1.04 (1.00–1.08)	0.041	1.02 (0.98–1.06)	0.333	1.03 (0.96–1.11)	0.446
Life Experiences Survey, lower	1.08 (1.02–1.20)	0.028	-	-	-	-	-	-
Perceived Stress Scale, lower	1.01 (0.98–1.05)	0.547	-	-	-	-	-	-
Connor-Davidson Resilience Scale, higher	1.01 (0.99–1.02)	0.155	1.01 (0.99–1.02)	0.375	-	-	-	-
Multidimensional Scale of Perceived Social Support, higher	-	-	-	-	1.03 (1.00–1.06)	0.027	1.05 (1.00–1.11)	0.036
Brief Psychiatric Rating Scale suicidality item, lower	1.09 (1.02–1.20)	0.011	1.11 (1.05–1.31)	0.008	1.10 (1.00–1.37)	0.049	-	-

The treatment steps were administered from antidepressant monotherapy (Step 1) to Step 4, every 3 weeks during 12 weeks considering overall effectiveness and tolerability. At the next step, Step 1 monotherapy continuation including dose adjustment or enter into Step 2, 3, and 4 composed of adding strategies of previous step with switching, augmentation, combination treatment. Antidepressants initiated, switched or combined were bupropion, desvenlafaxine, duloxetine, escitaloproam, fluoxetine, mirtazapine, paroxetine, sertraline, venlafaxine, and vortioxetine. Augmented drugs were buspiron, lithium, triiodothyronine, and atypical antipsychotics including aripirprazole, risperidone, olanzapine, quetiapine, and ziprasidone. Treatment strategies were continuing initial monotherapy (M), switching antidepressants (S), augmenting with other drugs (A), combination of other antidepressants (C), S+A, S+C, A+C, and S+A+C. OR, odds ratio; CI, confidence interval

Step 2 treatment, 226 (18.1%) received Step 3 treatment, and 74 (5.9%) received Step 4 treatment. Remission rates were 35.0%, 47.3%, 51.8%, and 55.4% for treatment Step 1, 2, 3, and 4, respectively. Baseline characteristics by 12-week remission status according to treatment steps are compared in Table 1. In patients received Step 1 treatment, remission was significantly associated with higher age and age at onset, lower scores on HADS-A, LES, PSS, and BPRS suicidality item, and higher scores on SOFAS and CDRS. In Step 2, remission was significantly associated with higher age, married marital state, higher age at onset, lower scores on HAMD, HADS-A, and BPRS suicidality item, and higher scores on EQ-5D, SOFAS, and CDRS. In Step 3, remission was significantly associated with absent atypical feature, higher age at onset, lower number of depressive episodes, family history of depression, higher scores on SOFAS and MSPSS, and lower BPRS suicidality item scores. In Step 4, remission was significantly associated with employed state, lower HAMD scores, and higher scores on SOFAS and MSPSS.

Independent predictors of remission by treatment steps

Results on multi-variate analyses for identifying independent predictors of remission by treatment steps are summarized in Table 2. In Step 1, higher SOFAS scores and lower scores on LES and BPRS suicidality item; in Step 2, higher SOFAS scores and lower BPRS suicidality item scores; in Step 3, higher MSPSS scores and lower BPRS suicidality item scores; and in Step 4, only the higher MSPSS scores were determined as predictors.

DISCUSSION

In this study with depressive outpatients receiving the 12-week stepwise psychopharmacotherapy based on early clinical decision-making considering measurements and patient preference, symptoms and function evaluated by various assessment scales rather than socio-demographic and clinical characteristics at baseline were identified as predictors of remission. However, there were differences in the associations for remission between scores on assessment scales and treatment steps.

Higher functional levels and less recent life stress, assessed by SOFAS and LES, respectively, predicted remission particularly in patients receiving lower treatment steps (Step 1 or 2). Functional levels have usually been treated as correlates of depression severity or treatment outcomes.[18,19] Only a few studies evaluated the predictive value of psychosocial function on depression remission,[20] although this was not a stepwise treatment. Our findings suggest that functional assessment at baseline could be useful for predicting remission particularly in short-term (up to 6 week) lower treatment steps. Associations between life stressors and depression treatment responses have been controversial in that some reported significant findings,[21] while others didn't.[22] Our findings may give a clue to this controversy in that associations between life stress and remission were significant only in very short-term (up to 3 week) monotherapy period, and then the associations lost significance with longer and higher treatment steps.

Rather, social support predicted remission in patients receiving higher treatment steps (Steps 3 and 4). This finding was in keeping with previous results reported associations between social support and treatment resistant depression and recurrence.[23,24] Suicidal severity predicted remission in most (94%) patients that received treatment Steps 1–3. Depressed patients with a higher suicidality were reportedly characterized by distinct biological characteristics.[25] Therefore, more intensive treatment with particular ongoing clinical attention would be needed in these patients.

The findings were limited by the naturalistic design and single study site evaluation, but are strengthened by large sample size and comprehensive assessments. This report suggests that multi-faceted evaluations at baseline could predict remission by treatment steps, which might serve grounds for personalized treatment of depression and future studies.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.30773/pi.2022.0160.

Availability of Data and Material

The data that support the findings of study are available from the corresponding author (JM Kim) upon reasonable request.

Conflicts of Interest

Jae-Min Kim declares research support in the last 5 years from Janssen and Lundbeck. Sung-Wan Kim declares research support in the last 5 years from Janssen, Boehringer Ingelheim, Allergan and Otsuka. Jae-Min Kim and Sung-Wan Kim, contributing editors of the *Psychiatry Investigation*, were not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

Concenptualization: Jae-Min Kim. Data curation: Yun-Tae Jin, Ha-Yeon Kim, Ju-Wan Kim, Min Jhon. Funding acquisition: Jae-Min Kim. Investigation: Yun-Tae Jin, Ha-Yeon Kim, Min Jhon. Methodology: Ju-Wan Kim, Ha-Yeon Kim, Sung-Wan Kim. Project administration: Yun-Tae Jin, Ha-Yeon Kim, Hee-Ju Kang. Resources: Sung-Wan Kim, Il-Seon Shin, Jae-Min Kim. Software: Ju-Wan Kim, Ha-Yeon Kim. Supervision: Jae-Min Kim. Validation: Ju-Yeon Lee, Sung-Wan Kim, Il-Seon Shin. Visualization: Ha-Yeon Kim, Ju-Wan Kim, Min Jhon, Hee-Ju Kang. Writing—original draft: Yun-Tae Jin, Jae-Min Kim. Writing—reviewing & editing: Ha-Yeon Kim, Min Jhon, Ju-Wan Kim, Ha-Yeon Kim, Ju-Yeon Lee, Sung-Wan Kim, Il-Seon Shin, Jae-Min Kim.

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Funding Statement

The study was funded by a grant of National Research Foundation of Korea Grant (NRF-2019M3C7A1031345 to Professor Jae-Min Kim.

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SUPPLEMENTARY MATERIAL 1

Eligibility criteria of the MAKE BETTER project

Inclusion criteria were: i) aged older than 7 years; ii) diagnosed with MDD, dysthymic disorder, or depressive disorder not otherwise specified (NOS), using the Mini-International Neuropsychiatric Interview (MINI),[1] a diagnostic psychiatric interview applying Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria;[2] iii) Hamilton Depression Rating Scale (HAMD)[3] score ≥14; iv) able to complete questionnaires, understand the objective of the study, and sign the informed consent form. Exclusion criteria were: i) an unstable or uncontrolled medical condition; ii) unable to complete the psychiatric assessment or comply with the medication regimen, due to a severe physical illness; iii) current or lifetime DSM-IV diagnosis of bipolar disorder, schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic disorder NOS, or other psychotic disorder; iv) history of organic psychosis, dementia, epilepsy, or seizure disorder; v) history of anticonvulsant treatment; vi) hospitalization for any psychiatric diagnosis apart from depressive disorder (e.g., alcohol/drug dependence); vii) electroconvulsive therapy received for the current depressive episode; viii) pregnant or breastfeeding. All participants reviewed the consent form and written informed consent was obtained. For participants aged under 16, written consent was obtained from a parent or legal guardian, and written assent was obtained from the participant.

Stepwise pharmacotherapy

Overall treatment steps and strategies are outlined in Supplementary Figure 1. Before treatment commencement, a comprehensive review was made of patients' clinical manifestation (e.g., psychotic or anxiety symptoms), severity of illness, physical comorbidity and medication profile, and history of previous treatments. In the first treatment Step 1, patients received antidepressant treatment, taking into consideration these data and treatment guidelines[4-6] for 3 weeks. Antidepressants used were bupropion, desvenlafaxine, duloxetine, escitaloproam, fluoxetine, mirtazapine, paroxetine, sertraline, venlafaxine, and vortioxetine. Initial starting doses were determined individually considering patients' age, body weight, and physical comorbidity and drug intake status. At week 1 and week 2 visits, antidepressant dosages were adjusted to optimise therapeutic benefit for each patient. After Step 1 antidepressant monotherapy, next step pharmacotherapy could be administered every 3 weeks during the 12-week treatment period, whenever needed.

At the end of Step 1 (week 3), overall effectiveness and tolerability were reviewed for proceeding with measurement-based next-step treatments. In cases of insufficient improvement (a HAMD score reduction of <30% from the baseline) or intolerable side effects, patients were instructed to choose whether they would prefer to remain in Step 1 monotherapy continuation including dose adjustment or enter into Step 2 strategies with switching, augmentation, or combination treatment. Pros and cons of each strategy were explained, and clinician opinion was provided, taking into considering both the patient's status and treatment guidelines.[4-6] Patients were also allowed to receive next-step treatment, if they were not fully satisfied with their current treatment for any reason and even if they showed sufficient improvement (a HAMD score reduction of ≥30% from the baseline) and absent/tolerable side effects. For determining treatment strategies, each patient's preference was given priority to maximize medication compliance and treatment outcomes.[7] Antidepressants switched or combined were bupropion, desvenlafaxine, duloxetine, escitaloproam, fluoxetine, mirtazapine, paroxetine, sertraline, venlafaxine, and vortioxetine. Augmented drugs were buspiron, lithium, triiodothyronine, and atypical antipsychotics including aripirprazole, risperidone, olanzapine, quetiapine, and ziprasidone.

At week 6, the same procedure as at week 3 was carried out to decide whether patients would remain in the same treatment steps or enter into further steps. Categories of treatment strategies in Step 3 were as follows: i) switch: antidepressant monotherapy switched from that in Step 2; ii) augmentation: switching augmented drugs from those received in Step 2; iii) combination: switching antidepressants added in Step 2; iv) switch + augmentation: either switching antidepressants at Step 2 and then adding augmentation drugs at Step 3, or adding augmentation drugs at Step 2 and then switching antidepressants at Step 3; v) switch + combination: either switching antidepressants at Step 2 and then combining other antidepressants at Step 3, or combining other antidepressants at Step 2 and then switching the antidepressant used from Step 1; vi) augmentation+combination: adding augmentation drugs at Step 2 and combining antidepressants at Step 3 or vice versa.

At week 9, the same procedure was repeated to decide whether patients would remain in the same treatment steps or enter into further steps. Categories of treatment strategy changes in Step 4 were as follows: i) switch: antidepressant monotherapy switched from Step 3; ii) augmentation: switching augmentation drugs from Step 3; iii) combination: switching antidepressants added in Step 3; iv) switch + augmentation: either twice switching antidepressants and once adding augmentation drugs, or one switch of antidepressant and two changes of augmentation drugs over the 4 steps; v) switch + combination: either twice switching antidepressants used from Step1 and once combining antidepressants, or once switching antidepressants used from Step 1 and twice changing combined drugs over the 4 steps; vi) augmentation + combination: either twice changing augmented drugs and once changing combined antidepressants, or once changing augmented drugs and twice changing combined antidepressants over the 4 steps; vii) switch + augmentation + combination: three strategies used simultaneously at the Step 4 regardless of the order of administered strategies in the previous steps.

Use of any anxiolytics/hypnotics (including alprazolam, bromazepam, clonazepam, clorazepate, diazepam, ethyl loflazepate, flunitrazepam, lorazepam, and zolpidem) was allowed at any of the time points of the study, whether this was to improve efficacy, relieve associated symptoms, or treat side effects.

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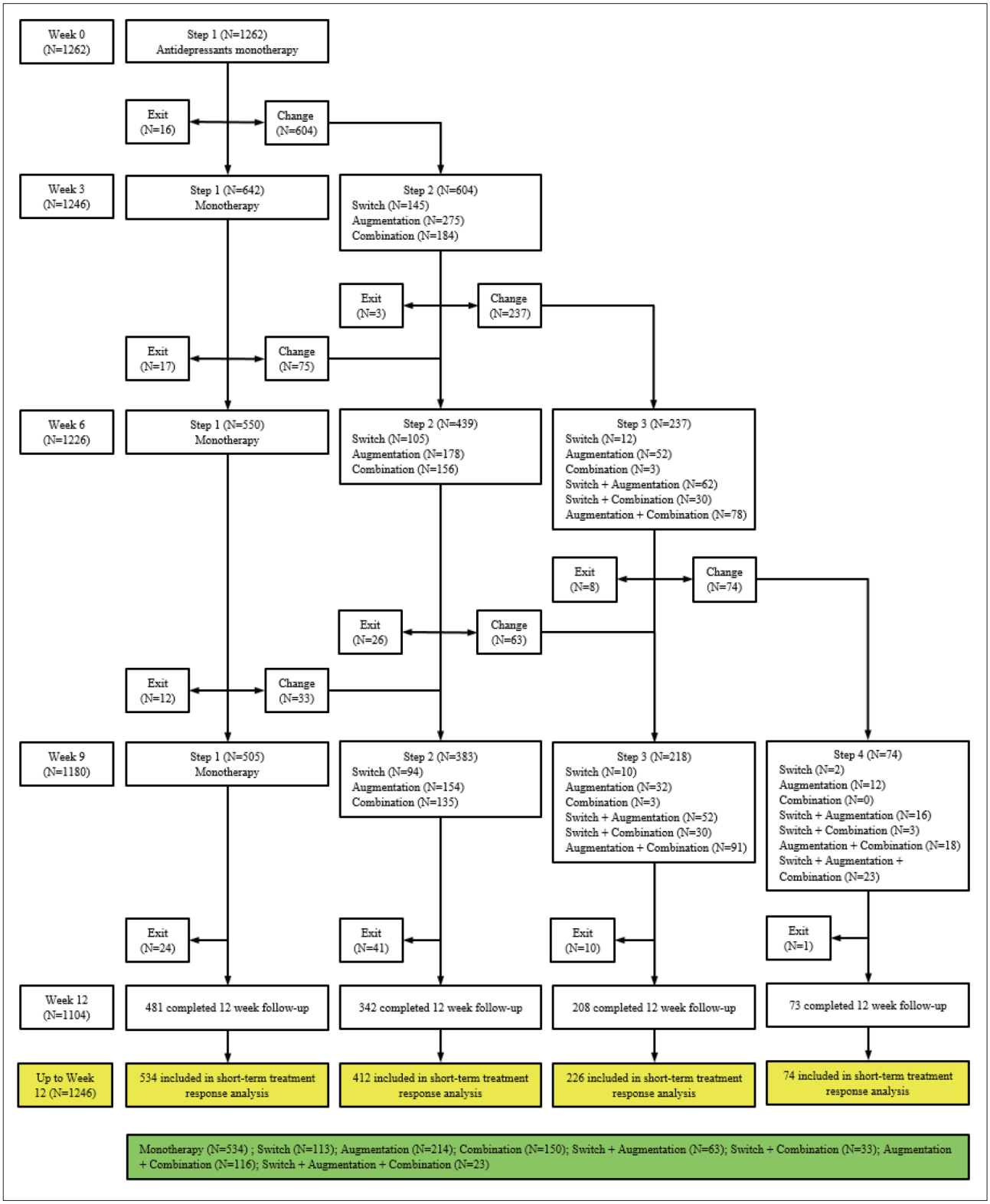

Supplementary Figure 1. Participant flow by treatment steps and strategies for 12-week outcomes. Antidepressants initiated, switched or combined were bupropion, desvenlafaxine, duloxetine, escitaloproam, fluoxetine, mirtazapine, paroxetine, sertraline, venlafaxine, and vortioxetine. Augmented drugs were buspiron, lithium, triiodothyronine, and atypical antipsychotics including aripirprazole, risperidone, olanzapine, quetiapine, and ziprasidone.Treatment strategies were continuing initial monotherapy (M), switching antidepressants (S), augmenting with other drugs (A), combination of other antidepressants (C), S+A, S+C, A+C, and S+A+C.