

A Pharmacogenomic-based Antidepressant Treatment for Patients with Major Depressive Disorder: Results from an 8-week, Randomized, Single-blinded Clinical Trial

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Objective: Pharmacogenomic-based antidepressant treatment (PGATx) may result in more precise pharmacotherapy of major depressive disorder (MDD) with better drug therapy guidance.

Methods: An 8-week, randomized, single-blind clinical trial was conducted to evaluate the effectiveness and tolerability of PGATx in 100 patients with MDD. All recruited patients were randomly allocated either to PGATx (n=52) or treatment as usual (TAU, n=48) groups. The primary endpoint was a change of total score of the Hamilton Depression Rating Scale-17 (HAMD-17) from baseline to end of treatment. Response rate (at least 50% reduction in HAMD-17 score from baseline), remission rate (HAMD-17 score ≤ 7 at the end of treatment) as well as the change of total score of Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER) from baseline to end of treatment were also investigated.

Results: The mean change of HAMD-17 score was significantly different between two groups favoring PGATx by -4.1 point of difference ($p=0.010$) at the end of treatment. The mean change in the FIBSER score from baseline was significantly different between two treatment groups favoring PGATx by -2.5 point of difference ($p=0.028$). The response rate (71.7% vs. 43.6%, $p=0.014$) were also significantly higher in PGATx than in TAU at the end of treatment, while the remission rate was numerically higher in PGATx than in TAU groups without statistical difference (45.5% vs. 25.6%, $p=0.071$). The reason for early drop-out associated with adverse events was also numerically higher in TAU (n=9, 50.0%) than in PGATx (n=4, 30.8%).

Conclusion: The present study clearly demonstrate that PGATx may be a better treatment option in the treatment of MDD in terms of effectiveness and tolerability; however, study shortcomings may limit a generalization. Adequately-powered, well-designed, subsequent studies should be mandatory to prove its practicability and clinical utility for routine practice.

KEY WORDS: Depressive disorder; Pharmacogenetic testing; Antidepressants; Precision medicine; Effects; Tolerance.

INTRODUCTION

Major depressive disorder (MDD) is a common, chron-

ic, debilitating mood disorder causing serious functional impairment and significantly decreased quality of life. Despite the pathophysiological mechanisms of MDD have not yet been clearly elucidated, various hypothesis including monoamine neurotransmitters, neurotrophic factors, hormones, neurogenesis/neuronal plasticity, inflammation, genetics, and environmental factors have been proposed as the possible etiologies.

Diverse treatment modality such as antidepressant, psychotherapeutic approach such as cognitive behavioral

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treatment, transcranial magnetic stimulation, deep brain stimulation, electroconvulsive therapy (ECT), and so on. Currently, the main biological treatment for MDD is various antidepressants such as selective serotonin reuptake inhibitors (SSRIs), dopamine-norepinephrine reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and noradrenergic and specific serotonin antagonists, and multimodal antidepressant which were mainly developed under a monoamine hypothesis.¹⁻³⁾

Despite the ultimate goal of antidepressant treatment for patients with MDD is to achieve full resolution of symptoms leading to the restoration of functional impairment and wellness of quality of life, it is very difficult to achieve this optimal goal in routine practice.^{2,4)} For instance, according to the results from the most largest and longest practical clinical study for MDD, “the Sequenced Treatment Alternatives to Relieve Depression (STAR*D)” trial,⁵⁾ the overall remission rates for the treatment steps were 28% after level 1 treatment, while it was decreased to 10% at level 4 treatment; the unadjusted cumulative remission rate was 67%.^{6,7)} Inadequate clinical outcomes as remission and response as well as higher relapse rates were reported in those who needed additional treatment levels during the naturalistic follow-up phase. A number of meta-analyses have also consistently demonstrated potential limitation of efficacy in the use of antidepressants regardless of their action mechanisms (i.e., first generation antidepressants based on monoamine hypothesis vs. novel multimodal action mechanisms used for vortioxetine, etc.).^{8,9)}

Meanwhile the adherence of pharmacological treatment may be substantially influenced by adverse events (AEs) from antidepressants in patients with MDD, which is one of major obstacles for MDD treatment as well as linked to poorer outcome, in fact, almost half of patients with MDD were found to decline antidepressants due to AEs.¹⁰⁾

Recently the evidence proposing a critical role of genetic factors in the treatment variation has been substantially increasing, common genetic variants explain 42% of individual differences in antidepressant response in a recent genome-wide complex trait analysis, despite of limited and complex results from currently available genome wide association studies.¹¹⁾ Many independent pharmacogenetic studies which investigated some major genes involving pharmacokinetics (PKs) and pharmacody-

namics (PDs) as well as other pathways in central nervous system (CNS; i.e., neurotrophic factor, inflammatory factor, and signal transduction factors, etc.) in association with efficacy and side effects have been consistently reporting limited about promising benefits of pharmacogenomic-based treatment (i.e., *CYP2D6*, *CYP2C19*, *ABCB1*, *BDNF*, *SLC6A4*, *HTR2C*, *HTR2A*, etc.) in patients with MDD.¹²⁻¹⁴⁾ In addition, pharmacogenomic information about the medication dose adjustment, functional genomic information, relevant genomic markers, as well as drug interaction potential has been remarked in drug labels in western countries for some medications (i.e., tricyclic antidepressants, carbamazepine, and phenytoin, etc.).¹⁵⁻¹⁷⁾ In addition, pharmacogenetic testing has been also beneficial in saving of medical costs.¹⁸⁾

In addition, some pharmacogenomic-based treatment guidelines/algorithm have been also developed and continuously revised to catch up with rapid progress of modern pharmacogenomic findings.¹⁹⁻²¹⁾ The Clinical Pharmacogenetics Implementation Consortium (CPIC) has also continuously published updated-guidelines for drug selection and/or dosing of major antidepressants in the treatment of MDD.

Taken together, as a part of precision medicine, pharmacogenomic-based antidepressant treatment (PGATx) may offer more chance of remission and response as well as provide better tolerability since it deals with identification of patients at higher genetically-determined risk of AEs or poor response to antidepressants²²⁾ by integration and application of complex information from diverse different genes involving PKs and PDs.²³⁻²⁵⁾

Therefore, it is expected that this treatment approach may enhance clinical outcomes and improve safety issues in the use of antidepressant treatment in routine practice. Recently a number of commercially available and valid pharmacogenomic decision support kits exist in market as a part of precision medicine to minimize ‘trial and error’ and to have easy access to ‘right drug for right time’.²⁶⁻³⁰⁾ However, the complexity of antidepressants’ action mechanism and genetic etiology of MDD clearly limit the single gene phenotype testing. Hence the combinatorial PGATx involving such as PK-PK, PK-PD, and PD-PD gene interactions has been suggested to provide more advanced and improved pharmacogenomic testing.³¹⁾ Such commercial pharmacogenetic decision supporting tool kits (CPDSK) including genes involving CYP450 and other

candidate genes which get clinicians and patients easy access to better personalized medicine for treating MDD are available now days.²⁸⁾ However, a handful of PGATx studies with different methodologies^{21,30,32-38)} using CPDSK exist in the treatment of MDD mainly conducted in western countries, there has been a lack of such studies in Asia yet. Therefore, the present study aimed to evaluate the effectiveness and tolerability of commercial PGATx using Neuropharmagen[®] (AB-Biotics, S.A., Barcelona, Spain) vs. treatment as usual (TAU) in the present study in a Korean population.

METHODS

Study Design

The present study was a randomized, single-blind clinical trial to evaluate the effectiveness and tolerability of PGATx in 100 Korean patients with MDD. The effectiveness and tolerability of PGATx vs. TAU were directly compared for 8 weeks. The present study was conducted at two university-based teaching hospitals in Korea. All the subjects were blinded to their treatment group. To ascertain study integrity and assessment inter-reliability among raters, conferences on study description as well as education and training sessions were conducted twice before starting the study. Assessments were performed at screening (week -3 to 0), baseline (week 0), week 4, and week 8.

The study was approved by the relevant institutional review board (IRB) at each center and was conducted in compliance with the Declaration of Helsinki (IRB approval No., HC16EIMI0015). All patients provided informed consent. All study procedures were regularly audited and monitored by independent clinical research monitoring member.

Subjects

Diagnosis was based on clinical assessments by highly experienced and board-certified psychiatrists. The subjects included were at least 20 years old, met the diagnosis of MDD according to The Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) criteria. All study participants should meet the following criteria: 1) those who showed 3 or more on Clinical Global Impression-Improvement (CGI-I) score despite of current antidepressant treatment (mono- or polytherapy) with

proper dosage (based on drug label information) and duration (at least 6 weeks); or 2) intolerance to current antidepressant therapy based on clinicians' judgement.

Those who are not currently on antidepressant treatment were excluded in the study. Patients were also excluded if they were pregnant or nursing or if they reported substance abuse or dependence within the past 12 months. Additionally, patients diagnosed with unstable medical or neurological disorders were excluded (participation was allowed if the clinical condition was stable for more than 3 months under routine therapeutic medications, e.g., hypertension). Followings were also excluded from the study; 1) Those who have a current Axis I diagnosis of delirium, dementia, amnesic or other cognitive disorder, schizophrenia or other psychotic disorder, bipolar I or II disorder, eating disorder, obsessive-compulsive disorder, panic disorder, or posttraumatic stress disorder; 2) Those who have a clinically significant current Axis II diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder; 3) Those who experience hallucinations, delusion, or any psychotic symptomatology in the current depressive episode; 4) Those who have had formal cognitive-behavioral therapy or other psychotherapy; 5) Those who have participated in a clinical trial within the past month; 6) Those who have been hospitalized within 8 weeks of the first visit, and 7) Those who had ECT within 8 weeks of the first visit.

Study Procedure

Saliva sample collection, pharmacogenetic analysis, and Neuropharmagen[®] pharmacogenetic report

At screening visit, the study nature was explained to all subjects who gave informed consent and included in the study. The subject's demographics, clinical information and medical history as well as complete medical/neurological examination were also performed. A saliva sample for DNA extraction and genotyping of the genetic polymorphisms was collected from each subject with the amount indicated at the sample collection kit which was provided by ABBiotics SA (Barcelona, Spain). The sample kit includes all the material and documents to collect the sample and order the test. The saliva sample was consecutively sent to the laboratory of ABBiotics SA via airmail within two days after collection, genotyped, and finally

analyzed by integration of multiple information between neuropsychotropic drugs and pharmacogenetic profile for a production of client-friendly Neuropharmagen[®] pharmacogenetic report (NPR) at the same central laboratory.

In detail, the Neuropharmagen[®] genotyping test was able to analyze 22 antidepressants (agomelatine, amitriptyline, bupropion, citalopram, clomipramine, desipramine, desvenlafaxine, doxepine, duloxetine, escitalopram, fluvoxamine, fluoxetine, imipramine, mianserine, mirtazapine, nortriptyline, paroxetine, sertraline, trimipramine, trazodone, venlafaxine, and vortioxetine), 13 antipsychotics, 13 mood stabilizers and anticonvulsants, 6 antianxiety medications, and 5 other neuropsychotropic drugs with pharmacogenetic markers validated by either United States Food and Drug Administration (FDA), the CPIC or the Dutch Pharmacogenetics Working Group from the Royal Dutch Pharmacists Association (KNMP) at the time of the present study.

The final results were available with the NPR which was composed of followings: 1) graphic summary table indicated according to the four color code in relation to the use of specific neuropsychotropic medications described before based on integration of pharmacogenetic information: green (increased likelihood of positive response and/or lower risk of adverse drug reactions), red (increased risk of adverse drug reactions), yellow (need for drug dose monitoring and/or less likelihood of positive response), and white (described as standard, no genetic variants relevant to the treatment have been found, use as directed); 2) detailed pharmacogenomic data derived from the analysis of genetic polymorphisms in 30 genes associated with drug efficacy, specific AEs, and metabolism (CYP450 enzyme genes profile); and 3) additional information about the biological role of the genes and genetic variants found in the analysis that may influence the patient's response to drugs. The pharmacogenotyping result (available within 14 days after collection of saliva) was accessible through a web-based computer-aided system (<http://international.neurofarmagen.com>) which was notified to the investigator only via personal email and secured by the assigned exclusive ID and password, provided by ABBiotics SA, while all the subjects were blinded to their results until complete finalization of the present study. For each antidepressant, the NPR provided a summary recommendation of specific antidepressant se-

lection based on the analyzed pharmacogenetic results as seen in Supplementary Fig. 1 (available online only). The Supplementary Fig. 1 represent the first part of client-friendly and graphic summary of the results for easy use of the study results for busy clinicians in routine practice.

Treatment

All subjects meeting all inclusion/exclusion criteria were randomized to either PGATx or TAU groups at baseline (week 0). Randomization was stratified by study center with a 1:1 ratio for PGATx and TAU group, with the use of a random list generated by a computer. At baseline visit, antidepressant was selected based on the result of NPR in PGATx group, while TAU group received antidepressant under the discretion of investigator based on his (her) clinical experience and preference as well as individual patient's clinical factors and pharmacological history. All the subjects continued to receive the same antidepressant with flexible dose as indicated in drug label information throughout the study period. Benzodiazepines and sleeping pills (e.g., lorazepam, alprazolam, triazolam, zolpidem, etc.) could be used within the usual dose ranges when the patients were already on those medication at the time of enrolment as routine clinical practice. New use of the following drugs was prohibited throughout the study period: any combination of other new antidepressant, antipsychotics, mood stabilizers, CNS stimulant and anti-addiction agents. Subjects should be discontinued from the study whenever they would like to do so and defined early discontinuation criteria were also established in the study protocol (i.e., poor compliance, withdrawal consent, and lost follow up, suicide risk, etc.).

Assessment

Effectiveness and tolerability

The primary endpoint was the mean change of total score of the 17-item Hamilton Depression Rating Scale (HAM-D) from baseline to end of treatment. The change of total score of the Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER) from baseline to end of treatment was co-primary endpoint.

The secondary endpoints included the response and remission rates at the end of treatment: 1) response was de-

defined as a reduction in HAMD total score of at least 50% at the end of treatment from baseline and 2) remission was defined as an absolute HAMD total score of ≤ 7 at the end of treatment. Other secondary endpoints included the changes of Patient Health Questionnaire-9/-15 (PHQ-9/15), Clinical Global Impression-Severity (CGI-S) score, the changes of General Anxiety Disorder-7 (GAD-7) total score, and Sheehan Disability Scale (SDS), from baseline to end of treatment. The proportion of patients showing 1 or 2 in the Clinical Global Impression-Improvement (CGI-I) score at the end of treatment was also secondary effectiveness measure.

Any untoward medical occurrence in a subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, were defined as AE. All AEs were reported throughout the study; the use of the Systematic Assessment for Treatment Emergent Events-Systematic Inquiry (SAFTEE) ensured systematic collection of AE data.

All the effectiveness and tolerability measures were assessed at screening phase, baseline visit, week 4, and week 8.

Statistical Analysis

Continuous data were summarized by descriptive statistics (i.e., number of subjects, mean, and standard deviation) for treatment groups. Differences between two groups were analyzed using two sample *t* tests or Wilcoxon rank-sum tests if the assumption of normality was violated. Analysis of covariance (ANCOVA models) adjusted for baseline, center, and other important covariates were adopted for the analyses of continuous effectiveness data. Categorical data were summarized by frequency and percentage by treatment group. Differences in proportions between the two groups were analyzed using chi-square, Fisher's exact, or Cochran-Mantel-Haenszel (CMH) test, where appropriate.

The primary endpoints, mean change from the baseline to the end of treatment in HAMD and FIBSER total score, were evaluated by analysis of covariance (ANCOVA), with the total score at baseline as a covariate and study center as main effects. The response and remission rates as well as proportion of patients who scored 1 or 2 in the score of CGI-I at the end of treatment were evaluated using a CMH general association test, controlling for study center.

The mean changes in scores of CGI-S, SDS, PHQ-9/15, and GAD-7 from baseline to the end of treatment were evaluated using ANCOVA, with the score at the baseline as covariate and study center as main effects.

The proportion of subjects who scored 3 or more at FIBSER scale at the end of treatment was also compared by CMH general association test, controlling for study center. No formal statistical testing was applied to the incidences of subjects with AEs or potentially clinically significant abnormalities in vital signs.

To compute sample size for continuous variables, it was necessary to obtain an estimate of the population standard deviation of the variable (s) and the magnitude of the difference (d) the investigator wishes to detect. Assumed that the difference of HAMD between PGATx and TAU would be (d) 3.0 and standard deviation (s) 5.0, we needed need 90 completers in the study, with two-tailed test at significance level of 0.05 and 80% power. Hence, putting 10% early dropout rate, final sample was approximately 100 patients in total.

The intention-to-treat (ITT) population consisted of all patients who had at least one post-treatment assessment for effectiveness during the study. The effectiveness evaluation was based on the analyses with ITT on last observation carried forward.

RESULTS

Subjects

A total of 100 patients (PGATx, 52 vs. TAU, 48) were enrolled and took at least one dose of medication during the study. Figure 1 presents the subjects' disposition during the study.

The baseline clinical and demographic characteristics of subjects are presented in Table 1. Briefly, patients in both groups had moderate-to-severe MDD symptoms measured by HAMD total scores (23.8 ± 4.8). Middle-aged, married, and unemployed females predominated in both groups. The duration of illness was approximately 6 years in both groups. Approximately 10% of patients had prior history of admission for treatment of their MDD in both groups. All the patients had at least two or more previous failed antidepressant treatment history for current MDD episode.

There were no significant treatment group differences for any baseline demographic findings including employ-

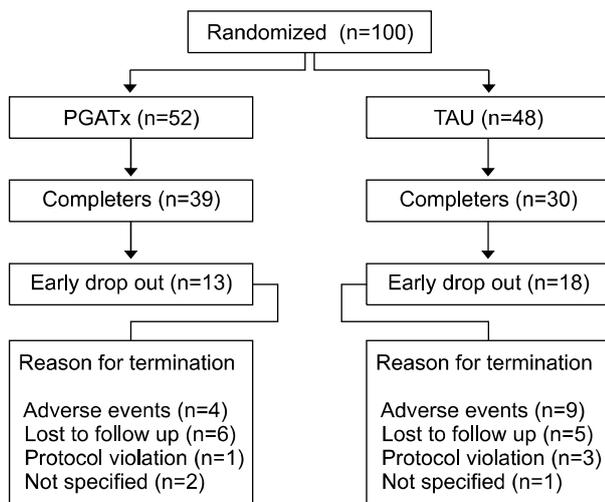


Fig. 1. The disposition of the subjects during the study.

ment, religion, and economic status and so on. Likewise, there were no significant treatment group differences for any clinical characteristics such as depressive symptomatology, family history of psychiatric diagnosis, somatic symptoms, and functional impairment, and so on.

Treatments

The most frequently selected antidepressants were serotonin norepinephrine reuptake inhibitors (SNRIs) followed by SSRIs, dopamine norepinephrine reuptake inhibitor (DNRI), and others in the PGATx group, while SSRIs were the most frequently selected antidepressants followed by SNRIs, others, and noradrenergic specific serotonin antagonist in the TAU group. However, there was no statistical difference in the distribution of antidepressants used in the study between the two treatment groups.

Primary Endpoints

The mean change of HAMD score was significantly different between two groups favoring PGATx by -4.1 point of difference ($p=0.010$) at the end of treatment (Table 2). The mean change in the FIBSER score from baseline was significantly different between two treatment groups favoring PGATx by -2.5 point of difference ($p=0.028$) (Table 2).

Secondary Endpoints

The response rate based on HAMD total score were also significantly higher in PGATx than in TAU at the end of

Table 1. Baseline characteristics of the subject in the study

Characteristic	PGATx (n=52)	TAU (n=48)	p value
Age (yr)	44.2±16.1	43.9±13.8	0.933
Sex, female	40 (76.9)	35 (72.9)	0.653
Onset age (yr)	36.9±15.5	38.6±14.2	0.604
Age at first diagnosis of MDD (yr)	48.3±7.5	41.2±13.5	0.270
Number of admission	1.1±0.7	1.4±0.5	0.506
History of admission	6 (11.5)	5 (10.4)	1.000
Number of previous antidepressant trial for current episode	2.5±2.2	2.1±1.5	0.295
Family history of psychiatric disorders, Yes	10 (19.2)	8 (16.7)	0.687
Job, Yes	11 (21.2)	14 (29.2)	0.328
Status of marriage			0.412
Married	23 (44.2)	26 (54.2)	
Single	12 (23.1)	12 (25.0)	
Separation	0 (0.0)	1 (2.1)	
Spouse death	1 (1.9)	1 (2.1)	
Not answered	4 (7.7)	4 (8.3)	
Religion, Yes			0.296
Christian	3 (5.8)	6 (12.5)	
Buddhism	3 (5.8)	6 (12.5)	
Catholic	8 (15.4)	4 (8.3)	
None	29 (55.8)	28 (58.3)	
Economic status (covered by livelihood protection)	11 (21.2)	12 (25.0)	0.238
Type of MDD			0.362
Melancholic	39 (75.0)	43 (89.6)	
Atypical	13 (25.0)	8 (16.7)	
Others	0 (0.0)	1 (2.1)	
Antidepressants			0.064
SSRI	16 (30.8)	21 (43.8)	
SNRI	24 (46.2)	18 (37.5)	
DNRI	7 (13.5)	1 (2.1)	
NaSSA	0 (0.0)	3 (6.3)	
Others	5 (9.2)	5 (10.4)	
HAMD	24.5±4.6	23.1±5.0	0.159
CGI-S	4.9±0.8	4.6±0.7	0.063
PHQ-9	20.9±3.8	19.1±5.3	0.065
PHQ-15	11.4±4.9	10.5±5.8	0.368
GAD-7	8.7±5.0	7.6±4.6	0.256
SDS	17.3±8.5	15.9±7.7	0.387

Values are presented as mean±standard deviation or number (%). PGATx, pharmacogenetic-based antidepressant treatment; TAU, treatment as usual; MDD, major depressive disorder; SSRI, serotonin selective reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; DNRI, dopamine and norepinephrine reuptake inhibitor; NaSSA, noradrenergic specific serotonin antagonist; HAMD, the 17-item Hamilton Depression Rating Scale CGI-S, Clinical Global Impression-Severity; PHQ-9/15, Patient Health Questionnaire-9/15; GAD-7, General Anxiety Disorder-7; SDS, Sheehan Disability Scale.

treatment by 28.1% difference ($p=0.014$), while the remission rate was numerically higher (19.9% difference) in

Table 2. Summary of the primary and secondary endpoints in the study

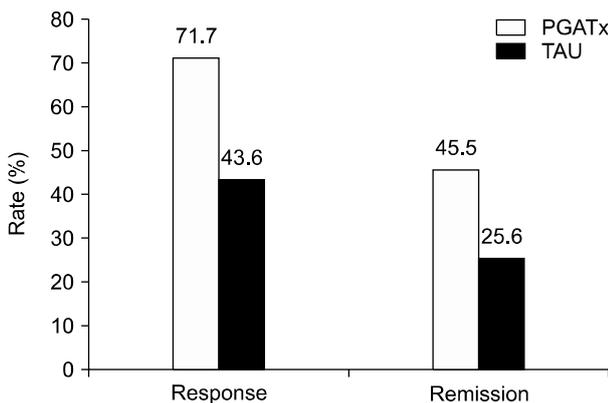
Endpoints	PGATx (n=52)	TAU (n=48)	F value	<i>p</i> value
HAMD [†]	-16.1±6.8	-12.1±8.2	6.818	0.010
FIBSER [†]	-4.1±5.3	-1.6±5.9	4.989	0.028
PHQ-9 [†]	-13.6±6.8	-9.8±7.8	6.656	0.011
PHQ-15 [†]	-8.1±5.0	-6.4±6.8	2.055	0.155
CGI-S [†]	-3.3±1.4	-2.3±1.8	9.755	0.002
GAD-7 [†]	-6.2±4.9	-4.1±4.7	4.696	0.033
SDS [†]	-9.9±7.8	-6.3±9.0	4.007	0.048
The proportion of patients showing 1 or 2 in the CGI-I score ^{*,†}	37 (80.4)	28 (60.9)	-	0.66

Values are presented as mean±standard deviation or number (%).

PGATx, pharmacogenetic-based antidepressant treatment; TAU, treatment as usual; PHQ-9/15, Patient Health Questionnaire-9/15; CGI-S, Clinical Global Impression-Severity; GAD-7, General Anxiety Disorder-7; SDS, Sheehan Disability Scale.

*Fisher's exact test; [†]The change from baseline to the end of treatment;

[‡]Proportion at the end of treatment.

**Fig. 2.** The response and remission rates between the two treatment groups at the end of treatment.

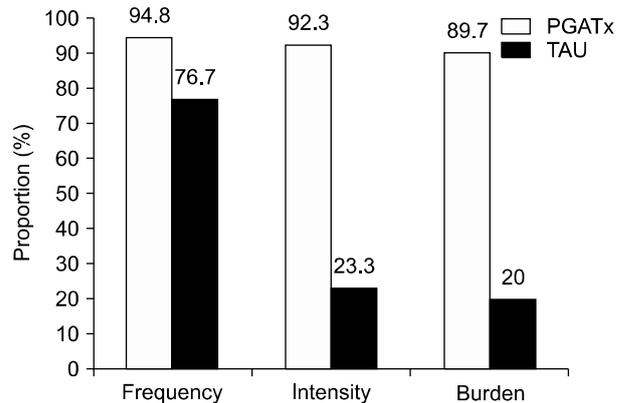
PGATx, pharmacogenomic-based antidepressant treatment; TAU, treatment as usual.

PGATx than in TAU groups without statistical difference ($p=0.071$) (Fig. 2).

The mean changes from baseline to the endpoint in PHQ-9 total scores in the PGATx and TAU were significantly different between the two groups favoring PGATx by -3.8 point of difference ($p=0.011$) (Table 2).

The mean changes from baseline to the endpoint in total CGI-S score in the PGATx and TAU were significantly different between the two groups favoring PGATx by -1.0 point of difference ($p=0.002$) (Table 2).

The mean changes from baseline to the endpoint in GAD-7 total scores in the PGATx and TAU were significantly different between the two groups favoring

**Fig. 3.** The proportion of patients those achieved 2 or less in Frequency, Intensity, and Burden of Side Effects Ratings sub-scores at the end of treatment.

PGATx, pharmacogenomic-based antidepressant treatment; TAU, treatment as usual.

PGATx by -2.1 point of difference ($p=0.033$) (Table 2).

The mean changes from baseline to the endpoint in SDS total scores in the PGATx and TAU were significantly but marginally different between the two groups favoring PGATx by -6.3 point of difference ($p=0.048$) (Table 2).

The proportion of patients showing 1 or 2 in the CGI-I score at the end of treatment was also significantly different between the two groups favoring PGATx by -2.1 point of difference ($p=0.039$) (Table 2).

However, the mean changes from baseline to the endpoint in PHQ-15 total scores in the PGATx and TAU were not significantly different between the two groups but numerically favoring PGATx by -1.7 point of difference ($p=0.155$) (Table 2).

The proportion of patients showing 2 or less in the FIBSER frequency ($p=0.0346$), intensity ($p=0.0001$), and burden ($p=0.0001$) sub-scores at the end of treatment was also significantly different between the two groups favoring PGATx by 18.1%, 69.0%, and 69.7% of differences (Fig. 3).

The study completion rate was numerically higher in PGATx (75.0%) than in TAU (62.5%); the reason for early drop-out associated with AEs was also numerically higher in TAU ($n=9$, 50.0%) than in PGATx ($n=4$, 30.8%) (Fig. 1).

The Table 3 represent the incidence of AEs between the two treatment groups in the study; the most common AE in the PGATx was sleep disturbance followed by anxiety, and somnolence, likewise it was sleep disturbance in the TAU, however, the next most common AE was headache

Table 3. Incidence of adverse events in the two treatment groups in the study*

Adverse event	PGATx (n=52)	TAU (n=48)
Sleep disturbance	16 (30.8)	15 (31.3)
Headache	6 (11.5)	13 (27.1)
Anxiety	12 (23.1)	11 (22.9)
Somnolence	8 (15.4)	10 (20.8)
Gastrointestinal discomfort	10 (19.2)	7 (14.6)
Dizziness	2 (3.8)	6 (12.5)
Dry mouth	6 (11.5)	6 (12.5)
Fatigue	3 (5.8)	3 (6.3)
Constipation	1 (1.9)	3 (6.3)
Increased appetite	1 (1.9)	2 (4.2)
Sexual dysfunction	1 (1.9)	1 (2.1)
Sweating	3 (5.8)	1 (2.1)
Skin rash	1 (1.9)	0 (0.0)
Dry eye	0 (0.0)	1 (2.1)
Extrapyramidal symptoms	0 (0.0)	1 (2.1)
Tinnitus	0 (0.0)	2 (4.2)
Concentration difficulty	1 (1.9)	0 (0.0)
Tremor	1 (1.9)	0 (0.0)

Values are presented as number (%).

*Safety population including all the subjects took at least one dose of medication during the study.

followed by anxiety and somnolence. Interestingly skin rash, concentration difficulty, and tremor were only presented in the PGATx group, while dry eyes, extrapyramidal symptoms, and tinnitus were merely observed in the TAU group during the study.

DISCUSSION

This is the first study to directly compare the clinical utility and benefit in the use of CPDSK, “Neuropharmagen[®]”, between PGATx and TAU treatment options in patients with MDD carrying inadequate antidepressant treatment outcomes despite of adequate doses and duration of treatment in East Asia. Overall, both treatments substantially improved the subjects’ depressive symptoms as measured by mean changes in total HAMD scores from baseline to the end of treatment. However, PGATx demonstrated superiority over TAU in term of effectiveness (measured by HAMD) and tolerability (measured by FIBSER); significantly more response rate and numerically more remission rate were also associated with PGATx than TAU at the end of treatment. Furthermore, PGATx was associated with significantly more improvement in most secondary endpoint (the changes of PHQ-9, SDS, CGI-S, and GAD scores from baseline to the end of treatment as well

as the proportion of patients showing 1 or 2 in the CGI-score) excluding the change of PHQ-15 score from baseline to the end of treatment. The overall incidences of AEs were comparable but the detailed profile was numerically different between the two treatment groups. Overall, the present findings suggest that PGATx may be associated with better treatment outcomes for MDD patients with inadequate antidepressant treatment responses relative to TAU, indicating that PGATx may be a potentially promising and valuable next treatment strategy for such patients.

Currently available many MDD treatment guidelines similarly propose switching, combination, and augmentation therapies when the patient is classified as inadequate or non-responder to ongoing antidepressant treatment in clinical practice.^{2,4,39-42} However, such alternative antidepressant treatment strategies have been also unsatisfactory to both clinicians and patients till today. In fact, remission was only 20% to 30% at level 1 and 2 treatment step; however, it decreased to 10% to 20% at level 3 and 4 treatment step during the STAR*D trial which reflected naturalistic treatment setting as well as being the most largest and longest practical clinical trials in the treatment of MDD.^{6,7} The STAR*D trials clearly suggested that the need for several steps to achieve remission for most patients in routine clinical practice. In addition, a recent large practical clinical trial evaluating whether antidepressant combination therapy is better than antidepressant monotherapy failed to find a superiority of combination treatment over monotherapy in terms of efficacy and safety (more safety issues and numerically less remission in combination therapy than monotherapy).⁴³ In addition, augmentation of atypical antipsychotics (AAs), particularly aripiprazole has been a popular supplementary therapy for those not meeting adequate antidepressant responses; however, MDD usually needs a long-term treatment with various psychotropics, suggesting a risk of developing unwanted motor AEs such as tardive dyskinesia that is prone to those with long-term exposure to antipsychotics.⁴⁴⁻⁴⁶ Therefore, PGATx may be a useful and viable treatment option for such difficult-to-treat patients with MDD since it pursuit a way of precision medicine maximizing a benefit but minimizing a risk via use of complex analyses of pharmacogenomics information involving basic pharmacogenomic information, specific target genes showing a critical role in drug responses, gene-gene interaction, and drug-drug interac-

tion.^{21,30,32-38)}

There have been only a handful of prospective and retrospective clinical studies investigating the utility of commercial and combinatorial pharmacogenomic testing on clinical outcomes in patients with MDD. In such studies, our results on effectiveness were comparable with those from other clinical trials as well as other studies without commercial pharmacogenomic testing.^{14,18,21,32,33,35-37,47)} In a recent 12 weeks, double-blind, multicenter PGATx study³²⁾ conducted in Spain, PGATx-guided treatment demonstrated a higher responder rate than TAU at the end of treatment with 12% difference, where the difference increased by 4% more when the subjects those did not follow PGATx recommendation were removed from the analysis, indicating the utility of PGATx treatment. Furthermore, such higher response rate was more profound and consistent in those with 1 to 3 failed drug trials. Such findings were sufficient to prove the clinical usefulness of PGATx upon the failure of the traditional first line of antidepressants. Regarding tolerability, the AEs burden was significantly higher in TAU group than in PGATx group based on the assessment of FIBSER score (odds ratio, 2.1). In a recent retrospective study (n=182),³³⁾ various psychiatric patients (i.e., MDD, bipolar disorder, schizophrenia, etc.) with PGATx treatment had four times higher odds of improvement in psychiatric symptoms compared to those without PGATx regardless of their diagnosis as well as such improvement was stable and sustained at 3 months follow-up visit. However, there were no differences in AEs rate between the two treatment groups due to small sample size, retrospective design, recall bias, and absolute small incidence of AEs rate during the study. Such findings were consistently reported from other pharmacogenomics studies used CPDSK where the odds ratios of response and remission rates ranged from 2 to 3.6 and 2.8 to 2.9, respectively.^{18,35-37)} With the respect of effectiveness, our study results were better than those from previous studies used Neuropharmagen[®], they may be caused by different characteristics of subjects (older and more mean numbers of antidepressant failure, etc.) and differences in blindness, regional differences in symptomatology in MDD,⁴⁸⁾ difference in genetic profile may contribute to such differential effects among studies. The mean numbers of antidepressant failure in our subjects were approximately at least 2 which is comparable to level 3 treatment of STAR*D trial, so that our subjects also

represent well naturalistic treatment setting in routine clinical practice.

However, our study has some shortcomings to be generalized in routine practice since the gold-standard of modern clinical trial is based on randomized, double-blind, multicenter study (i.e., two successful, randomized, double-blind, placebo-controlled, clinical trials are also required for approval of certain antidepressant by the FDA). Our study design was not strict double-blind but randomized and single-blind to the subject. Hence, observation bias by investigators between trial centers may not be fully excluded. However, well-designed and strict randomized clinical trials methodology has also underlying issues relative to design-specific biases.^{29,34,42,43)} Our findings of PGATx showed some promising antidepressants based on pharmacogenomics information in term of effectiveness and tolerability, however, the trial duration was too short to test such antidepressants which were not selected in the present study; additionally the present study design allowed only one antidepressant and did not allow subsequential alternative selection/trial of such remaining antidepressants for further extended period. That point should be reevaluated in next adequately-powered, well-designed study with the use of Neuropharmagen[®].

Approximately 40 CPDSK are currently available, in particular dominantly prevailing in the USA.⁴⁹⁾ However, the existence of significant variability of the frequencies in some valuable gene polymorphisms in the different populations is also well-known by which variation in the antidepressant responses between populations carrying the same polymorphism should be problematic in wide use of such CPDSK since such differential effects may be associated with a polygenic influence.^{42,50)} Despite of availability of more than 40 CPDSK, the agreement among such tool kits are still in debate. According to the recent pilot study which assessed the degree of agreement between such CPDSKs manufactured by four different companies with published data in the context of MDD treatment,²⁶⁾ the agreement in medication recommendations across the four CPDSKs was only modest, indicating substantial differences in the genes/variants tested, phenotyping strategies, and the algorithms used to predict drug-gene interactions among manufacturers; clearly such points suggest that we need a substantial progress in determination of genetic predictors as well as clinical studies investigating the clinical applicability of a genetic bio-

marker set.²⁵⁾

Finally, economic benefit with the use of PGATx should be one of important factor to be generalized in clinical practice, however, we did not include such effects in the present study; indeed, according to the recent study⁵¹⁾ investigating the direct and indirect cost-effectiveness of PGATx with the use of data from meta-analysis, the improved responsiveness by PGATx may be associated with substantial reduction of medical costs. Such economic benefit of PGATx has been consistently reported from multiple researches with different study design.^{52,53)}

In summary, the present study clearly demonstrated the clinical utility and benefit of a CPDSK in terms of effectiveness and tolerability in treating patients with MDD who had a history of multiple antidepressants failure. However, some limitations inherent to PGATx treatment should be considered (i.e., dependence on patient's clinical profile/genetic predisposition,⁵⁴⁾ ethnic variation on differential functional outcome,⁴⁹⁾ and basic critics that P450 genotype is just one of many factors that influence drug concentrations⁵⁵⁾).

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SUPPLEMENTARY MATERIALS

Supplementary data is available at <https://doi.org/10.9758/cpn.2018.16.4.469>.

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SUMMARY TABLE			
An initial interpretation of the results obtained from the patients genetic profile is displayed in a table below. For each drug examined, the result is indicated according to the following code:			
Standard	▶ No genetic variants relevant to the treatment have been found. Use as directed.	▶	Need for drug dose monitoring and/or less likelihood of positive response.
▶	Increased likelihood of positive response and/or lower risk of adverse drug reactions.	▶	Increased risk of adverse drug reactions.
Antidepressants			
Amitriptyline	▶	Bupropion	Standard
Clomipramine	▶	Desipramine	▶
Duloxetine	Standard	Escitalopram	Standard
Fluvoxamine	▶	Imipramine	▶
Mirtazapine	▶	Nortriptyline	▶
Sertraline	Standard	Trimipramine	▶
Citalopram	▶		
Doxepine	▶		
Fluoxetine	▶		
Mianserin	▶		
Paroxetine	▶		
Venlafaxine	▶		
Antipsychotics			
Aripiprazole	▶	Clozapine	▶
Olanzapine	▶	Perphenazine	▶
Risperidone	▶	Thioridazine	▶
Zuclopentixol	▶		
Haloperidol	▶		
Quetiapine	Standard		
Ziprasidone	▶		
Stabilizers and anticonvulsants			
Carbamazepine	▶	Clobazam	Standard
Lamotrigine	Standard	Levetiracetam	Standard
Lorazepam	▶	Oxcarbazepine	Standard
Phenytoin	▶	Pregabalin	Standard
Valproic Acid	Standard	Vigabatrin	Standard
Clonazepam	Standard		
Lithium*	▶		
Phenobarbital	Standard		
Topiramate	Standard		
Others			
Atomoxetine	▶	Methadone	Standard
Naloxone	Standard	Naltrexone	Standard
Methylphenidate	▶		
Pramipexol	▶		

Supplementary Fig. 1. Neuropharmagen[®] (AB-Biotics, S.A., Barcelona, Spain) pharmacogenetic report (NPR) used in the study.