Section: Miscellaneous

Original Research Article

PROSPECTIVE EVALUATION OF PHARMACOGENOMIC-GUIDED ANTIDEPRESSANT THERAPY ON CLINICAL RESPONSE AND ADVERSE DRUG REACTIONS IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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ABSTRACT

Background: Major depressive disorder is a common and disabling psychiatric condition with considerable variation in treatment response and tolerability. Genetic differences in drug-metabolizing enzymes may influence antidepressant exposure, clinical effectiveness and the occurrence of adverse drug reactions. Pharmacogenomic-guided prescribing may therefore assist clinicians in selecting appropriate antidepressants and optimizing dosage. The aim is to prospectively evaluate the effect of pharmacogenomic-guided antidepressant therapy on clinical response, remission, functional outcomes and adverse drug reactions in patients with major depressive disorder.

Materials and Methods: This prospective, randomized, parallel-group, open-label, assessor-blinded comparative study included 220 patients with major depressive disorder at a tertiary care hospital. Patients were equally allocated to a pharmacogenomic-guided treatment group and a standard-treatment group, with 110 patients in each group. Pharmacogenomic testing included clinically relevant CYP2D6, CYP2C19 and CYP2B6 variants. Depression severity and functional outcomes were assessed using HAM-D-17, PHQ-9, Clinical Global Impression and Sheehan Disability Scale scores at baseline and during follow-up. Clinical response, remission, medication adherence, gene–drug interactions, treatment modifications and adverse drug reactions were compared. Data were analysed using IBM SPSS version 27.0.

Results: Baseline demographic and clinical characteristics were comparable between the groups. At least one actionable pharmacogenomic phenotype was identified in 69.09% of guided patients. At week 12, mean HAM-D-17 scores were significantly lower in the pharmacogenomic-guided group than in the standard-treatment group (7.86 ± 4.13 vs. 10.94 ± 4.56; $p<0.001$). Clinical response was achieved in 70.91% versus 52.73% of patients ($p=0.006$), while remission occurred in 45.45% versus 29.09% ($p=0.012$). Guided therapy was associated with earlier response, better adherence, fewer dose adjustments and fewer antidepressant switches. Clinically significant gene–drug interactions were lower in the guided group (7.27% vs. 26.36%; $p<0.001$). Adverse drug reactions occurred in 28.18% versus 46.36% of patients ($p=0.005$), and treatment discontinuation due to adverse effects was also significantly reduced.

Conclusion: Pharmacogenomic-guided antidepressant therapy improved clinical response, remission and functional recovery while reducing gene–drug interactions and adverse drug reactions. It may serve as a useful approach for individualized antidepressant selection and dosage optimization in major depressive disorder.

Keywords: Major depressive disorder; Pharmacogenomics; Antidepressants; Clinical response; Adverse drug reactions.

INTRODUCTION

Major depressive disorder (MDD) is a common, recurrent and disabling psychiatric illness characterized by persistent depressed mood, loss of interest or pleasure, cognitive disturbances, altered sleep and appetite, reduced energy and impaired social or occupational functioning. Its development reflects a complex interaction among genetic susceptibility, stressful life experiences, neuroendocrine dysregulation, altered neurotransmission, inflammation and changes in neural plasticity. The clinical presentation is heterogeneous, and patients with the same diagnosis may differ substantially in symptom pattern, severity, comorbidities, course and treatment requirements. This diversity makes individualized management essential and limits the effectiveness of a uniform therapeutic approach.[1] Despite the availability of psychological and pharmacological interventions, a considerable gap remains between the need for treatment and the delivery of adequate care. Delayed recognition, limited access to specialist services, stigma, poor adherence and premature discontinuation may contribute to persistent symptoms and recurrent episodes. Inadequately treated depression is associated with impaired quality of life, reduced productivity, strained relationships, increased healthcare utilization and elevated risk of self-harm. Improving the precision, acceptability and continuity of antidepressant treatment is therefore an important clinical and public-health priority.[2] Antidepressants, particularly selective serotonin reuptake inhibitors, serotonin–noradrenaline reuptake inhibitors and other newer agents, are central to the management of moderate-to-severe MDD. Treatment selection is conventionally based on symptom profile, previous response, comorbid illness, concomitant medication, anticipated adverse effects, patient preference and clinician experience. However, prescribing frequently involves sequential therapeutic trials because reliable predictors of individual response are limited. A medication that is effective and well tolerated in one patient may provide inadequate benefit or troublesome adverse effects in another, resulting in dose changes, switching, augmentation or discontinuation.[3] Variation in antidepressant outcomes is influenced by demographic, clinical, environmental and genetic factors. Pharmacokinetic variation is especially important because many antidepressants are metabolized by polymorphic cytochrome P450 enzymes. CYP2D6 and CYP2C19 contribute to the metabolism of several commonly prescribed antidepressants, while CYP2B6 has an important role for selected agents. Functional genetic variants may produce poor, intermediate, normal, rapid or ultrarapid metabolizer phenotypes. These phenotypes can alter drug exposure and may contribute to subtherapeutic concentrations, delayed response, concentration-related adverse reactions or early discontinuation.[4] Pharmacogenomics applies information regarding inherited genetic variation to support medication selection and dosage decisions. For serotonin reuptake inhibitor antidepressants, evidence-based recommendations are available for defined CYP2D6, CYP2C19 and CYP2B6 gene–drug pairs. Depending on the predicted phenotype and prescribed medication, recommendations may include a standard dose, lower starting dose, slower titration, enhanced monitoring or selection of an alternative drug. Pharmacogenomic information is intended to complement rather than replace clinical assessment, evaluation of drug interactions, therapeutic monitoring and shared decision-making.[5] Pharmacogenomic-guided prescribing may reduce avoidable trial-and-error treatment by identifying clinically relevant gene–drug interactions before or during antidepressant therapy. It may be useful when patients have experienced inadequate response, repeated adverse reactions, multiple medication changes or complex drug regimens. Nevertheless, available panels differ in gene coverage, tested variants, phenotype assignment and interpretation algorithms. Their clinical value may also depend on ancestry, medication selection, clinician adherence to recommendations and access to suitable alternatives. Carefully designed prospective studies are therefore required to evaluate effectiveness under routine clinical conditions.[6]

MATERIALS AND METHODS

This study was designed as a prospective, randomized, parallel-group, open-label, assessor-blinded comparative clinical study conducted in the Department of Psychiatry in collaboration with the Departments of Pharmacology, Clinical Genetics and Molecular Diagnostics at a tertiary care hospital. The study evaluated whether pharmacogenomic-guided selection and dose adjustment of antidepressant therapy improved clinical response and reduced adverse drug reactions in patients diagnosed with major depressive disorder compared with conventional antidepressant prescribing based on standard clinical judgement. Patients attending the psychiatry outpatient department or admitted to the psychiatry ward with a diagnosis of major depressive disorder were screened for eligibility. The diagnosis of major depressive disorder was established by a qualified psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders criteria and confirmed using a structured clinical interview. Patients fulfilling the eligibility criteria were enrolled after obtaining written informed consent. 220 patients were included in this study 110 in each group.

Inclusion Criteria

Patients aged 18–65 years of either sex with a confirmed diagnosis of major depressive disorder and a current major depressive episode were included. Eligible participants were required to have a baseline 17-item Hamilton Depression Rating Scale score of

18 or more, indicating at least moderate depressive symptoms. Patients who were antidepressant-naïve, required initiation of a new antidepressant or required a change in their existing antidepressant because of inadequate clinical response or intolerance were considered eligible. Only patients capable of understanding the study procedures, providing written informed consent and complying with clinical follow-up assessments were enrolled.

Exclusion Criteria

Patients with bipolar disorder, schizophrenia, schizoaffective disorder, primary psychotic disorders, substance dependence or a primary psychiatric diagnosis other than major depressive disorder were excluded. Patients with active suicidal intent requiring emergency psychiatric intervention or hospitalization, severe cognitive impairment, intellectual disability or an inability to provide informed consent were not enrolled. Pregnant or lactating women and patients with severe or uncontrolled hepatic, renal, neurological, endocrine or cardiovascular disease that could affect antidepressant selection or metabolism were excluded. Patients receiving electroconvulsive therapy during the current depressive episode, those with a previous pharmacogenomic test and patients taking medications known to produce clinically significant and unavoidable interactions with the selected antidepressants were also excluded.

Methodology: After completion of baseline clinical assessment and collection of the biological sample, eligible patients were randomly allocated in a 1:1 ratio to either the pharmacogenomic-guided treatment group or the standard treatment group. Randomization was performed using a computer-generated random sequence with variable block sizes. Group assignments were placed in sequentially numbered, opaque and sealed envelopes, which were opened only after enrolment. The psychiatrist prescribing the antidepressant was aware of treatment allocation because the pharmacogenomic report was required for treatment decisions in the intervention group. However, the investigator assessing depression severity, clinical improvement and adverse drug reactions remained blinded to group allocation.

Baseline Clinical Assessment: At enrolment, detailed demographic and clinical information was recorded using a predesigned case-record form. Demographic parameters included age, sex, residence, educational status, occupation, marital status, socioeconomic status and body mass index. Clinical parameters included age at onset of depression, duration of the current depressive episode, number of previous depressive episodes, family history of psychiatric illness, previous antidepressant exposure, history of inadequate treatment response, previous adverse drug reactions, psychiatric comorbidities, medical comorbidities, smoking status, alcohol consumption and concurrent medications.

Baseline severity of depression was assessed using the 17-item Hamilton Depression Rating Scale. Patient-reported depressive symptoms were measured using the Patient Health Questionnaire-9. Overall illness severity was evaluated using the Clinical Global Impression–Severity scale. Baseline anxiety symptoms, when present, were assessed using the Hamilton Anxiety Rating Scale. Functional impairment was evaluated using the Sheehan Disability Scale, which assessed impairment in occupational, social and family functioning.

Biological Sample Collection and DNA Extraction: After enrolment, approximately 3–5 mL of peripheral venous blood was collected from each participant under aseptic precautions in an ethylenediaminetetraacetic acid-containing tube. A buccal swab could be obtained when venous blood collection was not feasible. Samples were labelled with a unique study identification number and transported to the molecular diagnostic laboratory under recommended storage conditions. Genomic DNA was extracted using a validated commercially available DNA extraction kit according to the manufacturer's instructions. DNA quantity and purity were assessed using spectrophotometry, and samples not meeting the predefined quality requirements were re-extracted.

Pharmacogenomic Testing: Pharmacogenomic testing included clinically relevant genetic variants associated with antidepressant metabolism and treatment response. The core pharmacokinetic genes included CYP2D6, CYP2C19 and CYP2B6. Genotyping was performed using a validated real-time polymerase chain reaction-based allelic discrimination assay or an equivalent validated pharmacogenomic platform. Copy-number variation analysis was performed for CYP2D6 to identify gene deletions, duplications or multiplications wherever technically applicable.

Detected genetic variants were assigned to the corresponding star-allele diplotypes. Genotype-derived phenotypes were classified as poor, intermediate, normal, rapid or ultrarapid metabolizer phenotypes according to internationally accepted pharmacogenomic interpretation standards. Quality-control procedures included positive and negative controls in each analytical run, repeat testing of randomly selected samples, assessment of genotype call rates and verification of ambiguous or clinically significant results.

Pharmacogenomic Report and Treatment Recommendations: For patients allocated to the pharmacogenomic-guided group, the pharmacogenomic report was made available to the treating psychiatrist before initiation or modification of antidepressant treatment. The report included the detected genotype, predicted metabolizer phenotype, possible gene–drug interactions and recommendations regarding antidepressant selection, starting dose, dose titration or the need for enhanced clinical monitoring.

Antidepressants were categorized as having no clinically significant gene–drug interaction, a moderate interaction requiring dose modification or monitoring, or a clinically significant interaction for which an alternative antidepressant was preferred. Recommendations were based primarily on pharmacokinetic gene–drug relationships supported by recognized pharmacogenomic guidelines. The final treatment decision remained with the treating psychiatrist after considering symptom profile, previous treatment, comorbidities, concurrent medications, patient preference, cost and drug availability.

Pharmacogenomic-Guided Treatment Group: Patients in the pharmacogenomic-guided group received an antidepressant selected or adjusted according to their pharmacogenomic test results and relevant clinical characteristics. In patients identified as poor metabolizers, a lower starting dose, slower dose titration or an alternative antidepressant not predominantly metabolized by the affected enzyme was considered. In rapid or ultrarapid metabolizers, an alternative drug or clinically appropriate dose adjustment was considered because of the possibility of reduced drug exposure. Treatment changes, dose adjustments and the treating psychiatrist's acceptance or non-acceptance of the pharmacogenomic recommendation were documented.

Standard Treatment Group: Patients allocated to the standard treatment group received antidepressant therapy according to routine clinical practice. Antidepressant selection and dose titration were based on clinical presentation, baseline severity, comorbidities, previous treatment history, potential drug interactions, patient preference and the treating psychiatrist's judgement. Pharmacogenomic results were not disclosed to the treating psychiatrist during the outcome-assessment period. Patients in this group received the same clinical follow-up, counselling and supportive care as those in the pharmacogenomic-guided group.

Antidepressant Treatment and Concomitant Therapy: Patients in both groups received antidepressants approved for the management of major depressive disorder. The antidepressant class, drug name, initial dose, maximum achieved dose, dose modifications, switching of medication and augmentation strategies were documented. Short-term use of benzodiazepines or other supportive medications was permitted when clinically necessary, but their indication, dose and duration were recorded. Structured psychotherapy was permitted when equally accessible to both groups and was documented as a potential confounding variable. Major changes in psychotherapy or other psychotropic medications were avoided unless clinically indicated.

Follow-Up and Outcome Assessment: Participants were evaluated at baseline and at prespecified follow-up visits during antidepressant therapy, including assessments at weeks 2, 4, 8 and 12. At each visit, depressive symptom severity, global clinical improvement, medication adherence, dose changes, treatment discontinuation and adverse drug reactions were documented. The investigator responsible for administering the clinical rating scales remained unaware of treatment allocation.

The Hamilton Depression Rating Scale-17 and Patient Health Questionnaire-9 were administered at baseline and follow-up assessments. The Clinical Global Impression–Improvement scale was used to assess overall improvement after treatment initiation. Functional status was reassessed using the Sheehan Disability Scale. The time taken to achieve a clinically significant response and the number of antidepressant dose modifications or medication switches were also recorded.

Statistical Analysis: Data were entered into Microsoft Excel and analysed using IBM SPSS version 27.0. Continuous variables were expressed as mean ± standard deviation or median with interquartile range, while categorical variables were presented as frequencies and percentages. The independent-samples t-test or Mann–Whitney U test and chi-square or Fisher's exact test were used for group comparisons, as appropriate. Changes in depression scores were analysed using repeated-measures ANOVA, while logistic regression identified predictors of clinical response and adverse drug reactions. A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

A total of 220 patients diagnosed with major depressive disorder were enrolled in the present study and were equally randomized into the pharmacogenomic-guided treatment group (n=110) and the standard-treatment group (n=110).

[Table 1] presents the baseline demographic and clinical characteristics of the two study groups. The mean age of patients in the pharmacogenomic-guided group was 41.86 ± 11.24 years compared with 42.31 ± 10.98 years in the standard-treatment group, with no statistically significant difference (p=0.764). Females constituted a slightly higher proportion in both groups (56.36% and 54.55%, respectively), while males accounted for 43.64% and 45.45%, showing comparable gender distribution (p=0.786). The mean body mass index was similar between the groups (24.82 ± 3.76 vs. 25.09 ± 3.61 kg/m²; p=0.587).

The clinical characteristics were also well balanced between the two treatment groups. The mean duration of the current depressive episode was 7.42 ± 4.10 months in the pharmacogenomic-guided group and 7.58 ± 4.25 months in the standard-treatment group (p=0.777). Similarly, the mean number of previous depressive episodes was 1.78 ± 1.02 and 1.84 ± 1.08, respectively (p=0.672). Patients experiencing their first depressive episode constituted 41.82% in the pharmacogenomic-guided group and 39.09% in the standard-treatment group (p=0.680). Family history

of psychiatric illness, previous antidepressant exposure, previous adverse drug reactions and associated medical comorbidities were also comparable between the groups (all p>0.05).

[Table 2] summarizes the pharmacogenomic phenotype distribution and prescribing recommendations. The distribution of CYP2D6 metabolizer phenotypes was almost identical between the two groups (p=0.975). Normal metabolizers represented the largest subgroup, accounting for 60.00% of patients in the pharmacogenomic-guided group and 62.73% in the standard-treatment group. Intermediate metabolizers constituted approximately one-quarter of patients, while poor and ultrarapid metabolizers each represented about 7% of the study population.

A similar pattern was observed for CYP2C19 phenotypes, where normal metabolizers were the most frequent phenotype (44.55% and 46.36%), followed by intermediate metabolizers (24.55% and 22.73%). Poor, rapid and ultrarapid metabolizers were less common, and no statistically significant difference was observed between the study groups (p=0.995). Likewise, CYP2B6 phenotype distribution remained comparable (p=0.934), with more than 70% of patients classified as normal metabolizers.

[Table 3] demonstrates the changes in depression severity and functional outcome scores during follow-up. Baseline HAM-D-17 scores were comparable between the groups (23.84 ± 4.21 vs. 23.61 ± 4.08; p=0.681). By the second week, patients receiving pharmacogenomic-guided therapy demonstrated significantly lower HAM-D-17 scores than those receiving standard treatment (19.12 ± 4.36 vs. 20.31 ± 4.51; p=0.048). The difference became progressively larger throughout the study, with mean HAM-D-17 scores decreasing to 14.76 ± 4.58 versus 16.92 ± 4.72 at week 4, 10.18 ± 4.29 versus 13.42 ± 4.67 at week 8, and 7.86 ± 4.13 versus 10.94 ± 4.56 at week 12 (all p<0.001). The overall reduction from baseline was significantly greater in the pharmacogenomic-guided group (15.98 ± 5.02) compared with the standard-treatment group (12.67 ± 5.21; p<0.001).

Patient-reported depressive symptoms measured by PHQ-9 followed a similar trend. Although baseline PHQ-9 scores were comparable (17.92 ± 3.61 vs. 18.11 ± 3.55; p=0.694), significant improvement became evident from week 4 onwards. At week 12, the pharmacogenomic-guided group achieved a mean PHQ-9 score of 5.81 ± 3.31 compared with 8.20 ± 3.78 in the standard-treatment group (p<0.001).

[Table 4] compares the primary and secondary clinical outcomes between the two treatment groups. Follow-up completion rates were high in both groups, with 95.45% of patients in the pharmacogenomic-guided group and 93.64% in the standard-treatment group completing the 12-week assessment (p=0.553). Clinical response, defined as at least a 50% reduction in HAM-D-17 score, was achieved by 70.91% of patients receiving pharmacogenomic-guided therapy compared with 52.73% receiving standard treatment, representing a statistically significant improvement (p=0.006). Similarly, remission rates were significantly higher in the pharmacogenomic-guided group (45.45% vs. 29.09%; p=0.012).

An important finding was the marked reduction in clinically significant gene–drug interactions during treatment among patients managed using pharmacogenomic guidance (7.27% vs. 26.36%; p<0.001). Likewise, treatment-emergent adverse drug reactions occurred significantly less frequently in the pharmacogenomic-guided group (28.18% vs. 46.36%; p=0.005). Treatment discontinuation due to adverse effects was also significantly lower among patients receiving pharmacogenomic-guided therapy (6.36% vs. 14.55%; p=0.047).

[Table 5] presents the incidence and severity of treatment-emergent adverse drug reactions. Overall, adverse drug reactions were reported in 28.18% of patients receiving pharmacogenomic-guided therapy compared with 46.36% of patients treated according to standard clinical practice, demonstrating a statistically significant reduction in adverse events (p=0.005).

Among individual adverse drug reactions, gastrointestinal symptoms were the most frequently reported adverse effect in both groups, occurring in 10.00% of patients in the pharmacogenomic-guided group and 18.18% in the standard-treatment group, although the difference was not statistically significant (p=0.081). Similar trends favouring pharmacogenomic-guided therapy were observed for insomnia, somnolence, dizziness or headache, weight gain, tremor and agitation; however, none of these reached statistical significance (all p>0.05). Sexual dysfunction occurred significantly less frequently in the pharmacogenomic-guided group than in the standard-treatment group (6.36% vs. 14.55%; p=0.047).

Table 1: Baseline demographic and clinical characteristics of the study groups

Baseline parameter	Pharmacogenomic-guided group (n=110)	Standard-treatment group (n=110)	p-value
Age, years, mean ± SD	41.86 ± 11.24	42.31 ± 10.98	0.764
Male sex, n (%)	48 (43.64%)	50 (45.45%)	0.786
Female sex, n (%)	62 (56.36%)	60 (54.55%)	—
Body mass index, kg/m², mean ± SD	24.82 ± 3.76	25.09 ± 3.61	0.587
Duration of current episode, months, mean ± SD	7.42 ± 4.10	7.58 ± 4.25	0.777
Number of previous depressive episodes, mean ± SD	1.78 ± 1.02	1.84 ± 1.08	0.672
First depressive episode, n (%)	46 (41.82%)	43 (39.09%)	0.680
Family history of psychiatric illness, n (%)	31 (28.18%)	34 (30.91%)	0.658
Previous antidepressant exposure, n (%)	64 (58.18%)	67 (60.91%)	0.680

Previous adverse drug reaction, n (%)	22 (20.00%)	24 (21.82%)	0.740
Medical comorbidity, n (%)	28 (25.45%)	30 (27.27%)	0.760
HAM-D-17 score, mean ± SD	23.84 ± 4.21	23.61 ± 4.08	0.681
PHQ-9 score, mean ± SD	17.92 ± 3.61	18.11 ± 3.55	0.694
CGI-Severity score, mean ± SD	4.62 ± 0.71	4.57 ± 0.68	0.594
Sheehan Disability Scale score, mean ± SD	20.41 ± 4.88	20.73 ± 4.76	0.623

Table 2: Pharmacogenomic phenotype distribution and prescribing recommendations

Pharmacogenomic parameter	Pharmacogenomic-guided group (n=110)	Standard-treatment group (n=110)	p-value
CYP2D6 phenotype			0.975
Poor metabolizer	8 (7.27%)	7 (6.36%)	—
Intermediate metabolizer	28 (25.45%)	27 (24.55%)	—
Normal metabolizer	66 (60.00%)	69 (62.73%)	—
Ultrarapid metabolizer	8 (7.27%)	7 (6.36%)	—
CYP2C19 phenotype			0.995
Poor metabolizer	10 (9.09%)	9 (8.18%)	—
Intermediate metabolizer	27 (24.55%)	25 (22.73%)	—
Normal metabolizer	49 (44.55%)	51 (46.36%)	—
Rapid metabolizer	17 (15.45%)	18 (16.36%)	—
Ultrarapid metabolizer	7 (6.36%)	7 (6.36%)	—
CYP2B6 phenotype			0.934
Poor metabolizer	6 (5.45%)	5 (4.55%)	—
Intermediate metabolizer	25 (22.73%)	24 (21.82%)	—
Normal metabolizer	79 (71.82%)	81 (73.64%)	—
At least one actionable phenotype	76 (69.09%)	73 (66.36%)	0.665
Initial gene–drug interaction category			
No clinically significant interaction	51 (46.36%)	Not applicable	—
Moderate interaction requiring adjustment or monitoring	39 (35.45%)	Not applicable	—
Clinically significant interaction	20 (18.18%)	Not applicable	—
Pharmacogenomic-guided prescribing action			
No treatment modification required	48 (43.64%)	Not applicable	—
Antidepressant dose modified	30 (27.27%)	Not applicable	—
Alternative antidepressant selected	24 (21.82%)	Not applicable	—
Enhanced clinical monitoring advised	8 (7.27%)	Not applicable	—
Recommendation accepted by psychiatrist	96 (87.27%)	Not applicable	—
Final treatment pharmacogenomically concordant	94 (85.45%)	Not applicable	—

Table 3: Changes in depression severity and functional outcome scores during follow-up

Assessment parameter	Pharmacogenomic-guided group (n=110), mean ± SD	Standard-treatment group (n=110), mean ± SD	p-value
HAM-D-17 score			
Baseline	23.84 ± 4.21	23.61 ± 4.08	0.681
Week 2	19.12 ± 4.36	20.31 ± 4.51	0.048*
Week 4	14.76 ± 4.58	16.92 ± 4.72	<0.001*
Week 8	10.18 ± 4.29	13.42 ± 4.67	<0.001*
Week 12	7.86 ± 4.13	10.94 ± 4.56	<0.001*
Mean reduction from baseline	15.98 ± 5.02	12.67 ± 5.21	<0.001*
PHQ-9 score			
Baseline	17.92 ± 3.61	18.11 ± 3.55	0.694
Week 2	14.46 ± 3.49	15.38 ± 3.65	0.057
Week 4	10.88 ± 3.72	12.74 ± 3.88	<0.001*
Week 8	7.34 ± 3.46	9.85 ± 3.91	<0.001*
Week 12	5.81 ± 3.31	8.20 ± 3.78	<0.001*
Sheehan Disability Scale at week 12	9.62 ± 4.74	12.78 ± 5.08	<0.001*
CGI-Improvement score at week 12	2.11 ± 0.86	2.58 ± 0.94	<0.001*

Table 4: Comparison of primary and secondary clinical outcomes

Clinical outcome	Pharmacogenomic-guided group (n=110)	Standard-treatment group (n=110)	p-value
Completed week-12 assessment	105 (95.45%)	103 (93.64%)	0.553
Clinical response at week 12	78 (70.91%)	58 (52.73%)	0.006*
Clinical remission at week 12	50 (45.45%)	32 (29.09%)	0.012*
Mean time to response, weeks, mean ± SD†	6.41 ± 2.18	7.56 ± 2.43	0.005*
Medication adherence	94 (85.45%)	82 (74.55%)	0.043*
At least one dose adjustment	29 (26.36%)	44 (40.00%)	0.032*
Antidepressant switching	17 (15.45%)	30 (27.27%)	0.032*
Augmentation therapy required	15 (13.64%)	25 (22.73%)	0.080
Clinically significant gene–drug interaction during treatment	8 (7.27%)	29 (26.36%)	<0.001*
Any treatment-emergent adverse drug reaction	31 (28.18%)	51 (46.36%)	0.005*
Treatment discontinuation due to adverse effects	7 (6.36%)	16 (14.55%)	0.047*

Table 5: Distribution and severity of treatment-emergent adverse drug reactions

Adverse drug reaction	Pharmacogenomic-guided group (n=110)	Standard-treatment group (n=110)	p-value
Any adverse drug reaction	31 (28.18%)	51 (46.36%)	0.005*
Gastrointestinal symptoms	11 (10.00%)	20 (18.18%)	0.081
Insomnia	7 (6.36%)	15 (13.64%)	0.072
Somnolence	8 (7.27%)	14 (12.73%)	0.178
Dizziness or headache	6 (5.45%)	13 (11.82%)	0.093
Sexual dysfunction	7 (6.36%)	16 (14.55%)	0.047*
Weight gain	4 (3.64%)	10 (9.09%)	0.097
Tremor	3 (2.73%)	9 (8.18%)	0.075
Agitation	2 (1.82%)	7 (6.36%)	0.171
Maximum ADR severity			
Mild	20 (18.18%)	29 (26.36%)	0.145
Moderate	9 (8.18%)	18 (16.36%)	0.064
Severe	2 (1.82%)	4 (3.64%)	0.683
Probable causality according to Naranjo scale	24 (21.82%)	39 (35.45%)	0.025*
Possible causality according to Naranjo scale	7 (6.36%)	12 (10.91%)	0.230
Dose reduction required because of ADR	12 (10.91%)	23 (20.91%)	0.043*
Drug withdrawal or switching because of ADR	7 (6.36%)	16 (14.55%)	0.047*

DISCUSSION

The present prospective study included 220 patients with major depressive disorder, equally allocated to pharmacogenomic-guided treatment and standard treatment. Successful randomization was demonstrated by the absence of significant baseline differences in age, sex, body mass index, duration of the current episode, previous depressive episodes, family history, previous antidepressant exposure, medical comorbidities and baseline psychiatric scores. The mean baseline HAM-D-17 scores were 23.84 ± 4.21 and 23.61 ± 4.08, while the corresponding PHQ-9 scores were 17.92 ± 3.61 and 18.11 ± 3.55 in the pharmacogenomic-guided and standard-treatment groups, respectively. These findings ensured that subsequent differences were more likely attributable to the treatment strategy rather than baseline imbalance. Han et al. (2018) similarly randomized 100 patients to pharmacogenomic-based antidepressant treatment (n=52) or treatment as usual (n=48) and reported no significant baseline differences between the groups. Their pharmacogenomic-guided group subsequently demonstrated a significantly higher response rate than standard care at eight weeks (71.7% vs. 43.6%; p=0.014), supporting the importance of initially comparable groups when assessing pharmacogenomic effectiveness.[7] The pharmacogenomic analysis demonstrated substantial interindividual variation in genes involved in antidepressant metabolism. Normal metabolizers formed the largest CYP2D6, CYP2C19 and CYP2B6 subgroups; however, at least one clinically actionable phenotype was identified in 69.09% of patients in the pharmacogenomic-guided group and 66.36% in the standard-treatment group. In the guided group, 35.45% of patients had a moderate gene–drug interaction requiring dose adjustment or enhanced monitoring, while 18.18% had a clinically significant interaction favouring an alternative antidepressant. These findings indicate that although most patients were normal metabolizers for an individual gene, combinations of phenotypes, prescribed drugs and dosage requirements frequently produced clinically relevant prescribing information. Oslin et al. (2022), in the PRIME Care trial, similarly found that the estimated proportions of patients receiving antidepressants with no, moderate and substantial drug–gene interactions were 59.3%, 30.0% and 10.7% in the pharmacogenomic-guided group compared with 25.7%, 54.6% and 19.7% under usual care. Pharmacogenomic guidance increased the likelihood of receiving a drug with no rather than moderate or substantial interaction more than fourfold (OR=4.32; p<0.001).[8] Pharmacogenomic results produced meaningful changes in clinical prescribing in the present study. Antidepressant dosage was modified in 27.27% of patients, an alternative antidepressant was selected in 21.82%, and enhanced monitoring was advised in 7.27%. Treating psychiatrists accepted 87.27% of the recommendations, and 85.45% of patients ultimately received pharmacogenomically concordant treatment. The small difference between recommendation acceptance and final concordance may reflect clinical considerations such as previous response, comorbidities, concurrent medication, patient preference, affordability and drug availability. Hall-Flavin et al. (2013) also demonstrated that pharmacogenomic information substantially influenced medication management. Among patients initially taking a medication associated with a significant gene–drug interaction, medication changes or dose adjustments were made in 93.8% of guided patients compared with 55.6% of unguided patients (p=0.01). At the end of follow-up, 40.0% of guided patients were receiving a medication categorized as having no significant gene–drug interaction compared with 27.6% of patients receiving usual treatment. These findings support the clinical usefulness of converting laboratory results into clear and actionable prescribing recommendations.[9] Patients receiving pharmacogenomic-guided therapy demonstrated earlier and progressively greater improvement in

depression severity. Although baseline HAM-D-17 scores were similar, a significant difference appeared by week 2, when scores were 19.12 ± 4.36 in the guided group and 20.31 ± 4.51 in the standard-treatment group (p=0.048). By week 12, the respective scores had decreased to 7.86 ± 4.13 and 10.94 ± 4.56, with significantly greater mean reductions from baseline in the guided group (15.98 ± 5.02 vs. 12.67 ± 5.21; p<0.001). PHQ-9 scores followed the same pattern, reaching 5.81 ± 3.31 versus 8.20 ± 3.78 at week 12. Better Sheehan Disability Scale and CGI-Improvement scores further suggested that symptom reduction was accompanied by functional and global clinical improvement. Greden et al. (2019), in the 1,167-patient GUIDED trial, reported 27.2% symptom improvement with guided care compared with 24.4% under usual care at week 8 (p=0.107). Although mean symptom improvement was not significant, response rates were 26.0% versus 19.9% (p=0.013), and remission rates were 15.3% versus 10.1% (p=0.007). The larger symptom difference in the present study may relate to its 12-week assessment, high treatment concordance and differences in participant characteristics and prescribing algorithms.[10] The primary clinical outcomes strongly favoured pharmacogenomic-guided therapy. At week 12, 70.91% of patients in the guided group achieved a clinical response compared with 52.73% in the standard-treatment group, representing an absolute difference of 18.18 percentage points (p=0.006). Remission was achieved by 45.45% and 29.09%, respectively, producing an absolute difference of 16.36 percentage points (p=0.012). These differences indicate that approximately six patients would need to receive pharmacogenomic-guided therapy for one additional patient to achieve response or remission compared with standard treatment. Bradley et al. (2018) also reported significantly better outcomes among patients with depression receiving targeted pharmacogenetic guidance. At 12 weeks, the odds of achieving a treatment response were 4.72 times higher in the pharmacogenetically guided group than in the control group (OR=4.72; 95% CI: 1.93–11.52; p=0.001), while the odds of remission were 3.54 times higher (OR=3.54; 95% CI: 1.27–9.88; p=0.020).[11] In addition to improving response and remission, pharmacogenomic guidance appeared to optimize the treatment pathway. Patients in the guided group achieved response approximately 1.15 weeks earlier than those receiving standard treatment (6.41 ± 2.18 vs. 7.56 ± 2.43 weeks; p=0.005). Medication adherence was higher by 10.90 percentage points (85.45% vs. 74.55%; p=0.043), while subsequent dose adjustments (26.36% vs. 40.00%; p=0.032) and antidepressant switching (15.45% vs. 27.27%; p=0.032) were less frequent. This suggests that selecting an appropriate drug and dose at treatment initiation may reduce later trial-and-error changes. Winner et al. (2013) observed overall medication changes in 53% of pharmacogenomic-guided patients and 58% of controls (p=0.66); however, among patients initially receiving a medication with a severe gene–drug interaction, 100% of guided patients underwent an appropriate medication change compared with only 50% of controls (p=0.02). Response and remission also favoured guided treatment at week 10, at 36.0% versus 20.8% and 20.0% versus 8.3%, respectively.[12] The safety findings represent another important outcome of the present study. Clinically significant gene–drug interactions during treatment were substantially lower in the guided group than in the standard-treatment group (7.27% vs. 26.36%; p<0.001). Similarly, at least one treatment-emergent adverse drug reaction occurred in 28.18% of guided patients compared with 46.36% of controls (p=0.005), corresponding to an approximate 39% relative reduction. Treatment discontinuation because of adverse effects was also less frequent with pharmacogenomic guidance (6.36% vs. 14.55%; p=0.047). Shan et al. (2019) reported a smaller 8-week randomized study in which adverse-reaction rates were 55.56% in the guided group and 57.89% in the unguided group, without a statistically significant difference. Response rates of 74.19% versus 57.50% and remission rates of 61.29% versus 45.00% also favoured guidance but did not reach significance. Differences from the present findings may be explained by their smaller full-analysis sample of 71 patients, shorter follow-up, different gene panel and limited statistical power for safety outcomes.[13] The pattern of individual adverse reactions further supported improved tolerability with pharmacogenomic-guided prescribing. Gastrointestinal symptoms were most frequent in both groups but were lower with guided therapy (10.00% vs. 18.18%; p=0.081). Sexual dysfunction was significantly reduced from 14.55% under standard treatment to 6.36% with pharmacogenomic guidance (p=0.047), while insomnia, somnolence, dizziness, weight gain, tremor and agitation also showed nonsignificant trends favouring guided treatment. Probable adverse drug reactions according to the Naranjo scale were less frequent in the guided group (21.82% vs. 35.45%; p=0.025). Pharmacogenomic guidance also reduced dose reduction due to adverse reactions (10.91% vs. 20.91%; p=0.043) and drug withdrawal or switching (6.36% vs. 14.55%; p=0.047). Pérez et al. (2017) similarly reported better tolerability in a randomized trial involving 316 patients. Among patients with baseline side-effect burden, acceptable tolerability on the FIBSER scale was achieved by 66.7% of guided patients versus 50.0% of controls at week 6 and by 68.5% versus 51.4% at week 12 (OR=2.06; p=0.026).[14]

CONCLUSION

The present study demonstrated that pharmacogenomic-guided antidepressant therapy significantly improved clinical response, remission

and functional recovery in patients with major depressive disorder. It was also associated with earlier treatment response, better medication adherence and fewer dose modifications or antidepressant switches. Pharmacogenomic guidance significantly reduced clinically important gene–drug interactions, adverse drug reactions and treatment discontinuation due to intolerance. These findings support its use as a valuable tool for individualized antidepressant selection and dosage optimization in routine psychiatric practice.

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