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HOT TOPIC

Evaluating The Effectiveness of Pharmacogenomics-Based Care in Depression Compared to Standard Care: A Review of Current Evidence

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Abstract

Purpose of Review The purpose of this review is to evaluate how effective pharmacogenomic (PGx)-based care is in the treatment of depression. The clinical outcomes are also compared, such as response and remission rates with the current standards of care.

Recent Findings Multiple studies critically analyzed in this study showed mixed findings regarding the effectiveness of PGx-based care compared to current standard management. Symptomatic improvement is similar between the two strategies in the early stage of treatment, resulting in better response and remission rates, especially among patients treated with conventional-based therapy. PGx-based care, however, is noted to be more cost-effective for intractable cases of depression. The heterogeneity in the studies analyzed is minimal, making for consistent and general findings.

Summary PGx-guided care shows a promising alternative in improving the response and remission rates among patients with depression, especially among those with genetic variants that affect drug metabolism. Although it may not outperform the current standard of care in symptomatic relief in the early stage, its potential cannot be ignored. Reducing side effects and allowing for better selection strategies in treatment-resistant cases are added benefits. There is a need for long-term studies.

Keywords Pharmacogenomics · Depression · PGx testing · Response · Remission · Cost-effectiveness · Gene-drug interaction

Introduction

According to Hippocrates, health is regarded as a state of balance within the body, and disease is due to disturbance of this balance [1]. The ancient Greeks viewed mental health as a consequence of human interaction with their environment. Various influencing factors, such as diet, lifestyle, and living conditions, were considered determinants that could disturb this equilibrium within the body. They went further to study certain physical health conditions as manifestations of underlying mental health problems. For example, the presence of black bile was connected with a state of excessive melancholia.

Depression as a mental health crisis is regarded as one of the most recognized psychological disorders throughout history [2]. According to Kline, "more human suffering has resulted from depression than any other single disease affects humans" [3]. This is consistent in its presentation,

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though clinical presentation may differ in range and severity [4].

From the advent of psychiatry, the diagnosis of depression became more subjective and contextual. It was seen as a disproportionate response in terms of duration and severity to a particular circumstance [2] or without an appropriate cause [5]. It depended on the degree to which this response was understood about the surrounding events or circumstances. It was understood that depression, in contrast to typical

melancholy that occurs after one has had a tragic experience, was a pathologic response.

A German psychiatrist, Emil Kraepelin, played a key role in understanding concepts of depression, categorizing it along with mania as a component of manic-depressive illness. This classification later influenced the diagnostic framework currently employed in the Diagnostic and Statistical Manual of Mental Disorders (DSM) [6].

With the invention of traditional therapies like antidepressants, the 20th century witnessed remarkable progress in the treatment of depression. The "disease-centered theory" guided the development of these drugs, they addressed the biochemical imbalances in the brain that underlie depressive symptoms [7]. Chlorpromazine and other early antidepressants were first used as "neuroleptics," which produced drowsiness and were mainly used to treat psychosis [8]. By the 1950s, antidepressants were being reliably identified, and the discovery of Iproniazid was also a significant development [9]. Iproniazid's psychotropic effects were first observed in patients who reported feeling happier and more optimistic, being initially investigated as a therapy for tuberculosis. It inhibited monoamine oxidase, an enzyme that breaks down neurotransmitters like dopamine (DA), serotonin (5-HT), and norepinephrine (NE), according to later studies. Meanwhile this discovery, however, led to the development of monoamine oxidase inhibitors (MAOIs) [10], the first class of antidepressants, which were followed by the development of tricyclic antidepressants such as Imipramine and Amitriptyline [11]. By the 1970s and 1980s, selective serotonin reuptake inhibitors (SSRIs), which provide more specialized therapies with fewer adverse effects, were widely accessible. Later, these antidepressants were used to treat a variety of ailments, such as anxiety disorders, and chronic pain, increasing their clinical application and usefulness.

Despite these advancements, managing depression still remains arduous because patients' responses to medications vary widely. Many patients are often subjected to a trial-and-error process to determine the right drug and dosage, which delays the effectiveness of treatment and increases the risk of side effects [12]. This variability has sparked interest and eventually led to the adoption of precision medicine by scientists and clinicians, particularly pharmacogenomic (PGx) testing in psychiatric care. This approach uses genetic information to customize medication type and dosage tailored to each patient's condition and needs [13, 14]. PGx testing looks at genetic variations that affect drug metabolism and actions in the recipient's body, with the goal of improving treatment outcomes by minimizing side effects and maximizing efficacy. While the PGx testing has gained traction in various medical fields, its applications in psychiatry have been slower, partly due to differing perceptions of this approach and a lack of robust evidence supporting its widespread adoption. Nevertheless, it represents a promising option to address the limitations of traditional options for depression management, offering the potential for more precise and effective care. Hence, this study aims to evaluate the effectiveness of PGx-based care in depression when compared to the standard model of care involving the use of pharmacological therapies like antidepressants, psychological interventions such as cognitive behavioral therapy (CBT), and interpersonal therapy (IPT), or electroconvulsive therapy (ECT).

The rationale for pharmacogenomic (PGx) testing in depression

In managing depression, a physician makes a diagnosis based on clinical acumen and the use of selected diagnostic criteria. Most of the antidepressants currently in existence function by acting on monoamines in the brain. Clinical response is expected to occur within 2 to 3 weeks, but the effect is almost immediately seen in practice in certain instances. Furthermore, antidepressants of various classes are noted to have similar side effects. This brings the question of what the genomic targets of these drugs are. The serotonin transporter is a target receptor of SSRIs. Lesch et al. identified a polymorphism in the serotonin transporter gene (SLC6A4) that affects transcription efficacy [15], and individuals with short alleles of the 5-HTT gene-linked polymorphic region (5-HTTLPR) expressed reduced serotonin uptake. He demonstrated that long alleles of the 5-HTTLPR gene responded better to SSRIs. Smeraldi et al., in their study in Italy, showed that in depressed patients treated with fluvoxamine—SSRI, those with homozygous long alleges of the 5-HTTLPR showed a better response than those with heterozygous alleles [16]. This led to the conclusion that there was a relationship between the allergic variation and the 5-HTT gene promoter. Many more polymorphisms and genes should be considered.

PGx testing is increasingly used in psychiatry to individualize antidepressant treatment, particularly among patients with treatment-resistant depression or adverse drug reactions. This approach utilizes genetic material sources such as blood and saliva, which are collected in a laboratory to analyze key genes related to drug metabolism (e.g., CYP2D6,

CYP2C19) and response (e.g., SLC6A4, HTR2A). Following collection, the patient's DNA sample undergoes several processing procedures, including DNA extraction, purification, and genotyping. The results of genotyping are then sent to clinicians. This mechanism is often based on the cytochrome P450 (CYP) superfamily. The effectiveness of this enzyme system in metabolizing drugs, as well as a patient's response to medication, depends on their genetic makeup [35]. Targeting these genes, PGx testing reduces the likelihood of toxicity and enhances medication safety for both individual patients and the broader population. The assay can be used to analyze multiple genes simultaneously or to test a single gene. Despite the advantages of these advances, clinicians and researchers struggle to understand why the integration of PGx into psychiatry clinical practice has been notably slow. Although there are now numerous commercialized PGx tests for managing depressive patients, consistency is yet to be achieved on a larger population scale [36]. Additionally, there is limited research validating PGx testing across different ethnic and racial groups.

Objectives

- To evaluate the effectiveness of Pharmacogenomic-based care in treating depression.
- To compare treatment outcomes of Pharmacogenomic-based care versus standard care in treating depression.
- To provide evidence-based guidance for clinicians in leveraging PGx to improve the treatment of depression.

Methodology

Search Strategy

The literature search was conducted in the following databases: PubMed, Scopus, PsycINFO, Google Scholar, EMBASE, Cochrane Library, and Web of Science. The search aimed to include studies published between 2017 and 2024.

Search strategy employed combining keywords and Boolean operators to maximize retrieval of relevant studies. The search terms used in each database are as follows: "pharmacogenomic testing", "pharmacogenetics", "genomic medicine", "personalized medicine", "depression", "major depressive disorder", " MDD", "mental health", "standard care", "usual care", "effectiveness", "efficacy", "clinical outcomes", and "treatment outcomes."

We used Boolean operators (AND/OR) to refine our search and combine these keywords.

The period from 2017 to 2024 was chosen for our study inclusion to focus on the latest developments in PGx and its use in mental health. Over the past decade, research in this field has grown significantly, with most of its integration into clinical practice happening after 2017. This ensures the review covers up-to-date evidence and highlights recent progress in technology and clinical applications. **See** Figure 1 for more detailed information on the search strategy.

Inclusion and exclusion criteria

Inclusion criteria:

- Peer-reviewed original studies published between 2017 and 2024.
- Studies focusing on pharmacogenomic testing in the context of depression treatment.
- Comparisons between PGx-based care and standard care, with outcomes such as symptom improvement, adherence, and treatment effectiveness.
- Studies presenting quantitative or qualitative data.

Exclusion criteria:

- Non-English publications.
- Studies unrelated to depression or PGx-based care.
- Research focusing on theoretical models without clinical data.
- Reviews (including systematic reviews and meta-analysis), Conference abstracts, editorials, or articles lacking sufficient methodological rigor.

Data Extraction

A structured data extraction process was employed to collect relevant details from each study.

Extracted Data Elements:

- Study design and methodology.
- Population characteristics (e.g., sample size, demographics).
- Details of pharmacogenomic testing (e.g., type of test, genes analyzed).
- Outcomes measured (e.g., symptom reduction, cost-effectiveness, quality of life).
- Comparison between PGx-based care and standard care.

Screening Process:

1. Title and abstract screening to exclude irrelevant articles.

2. Full-text evaluation for eligibility and methodological rigor.

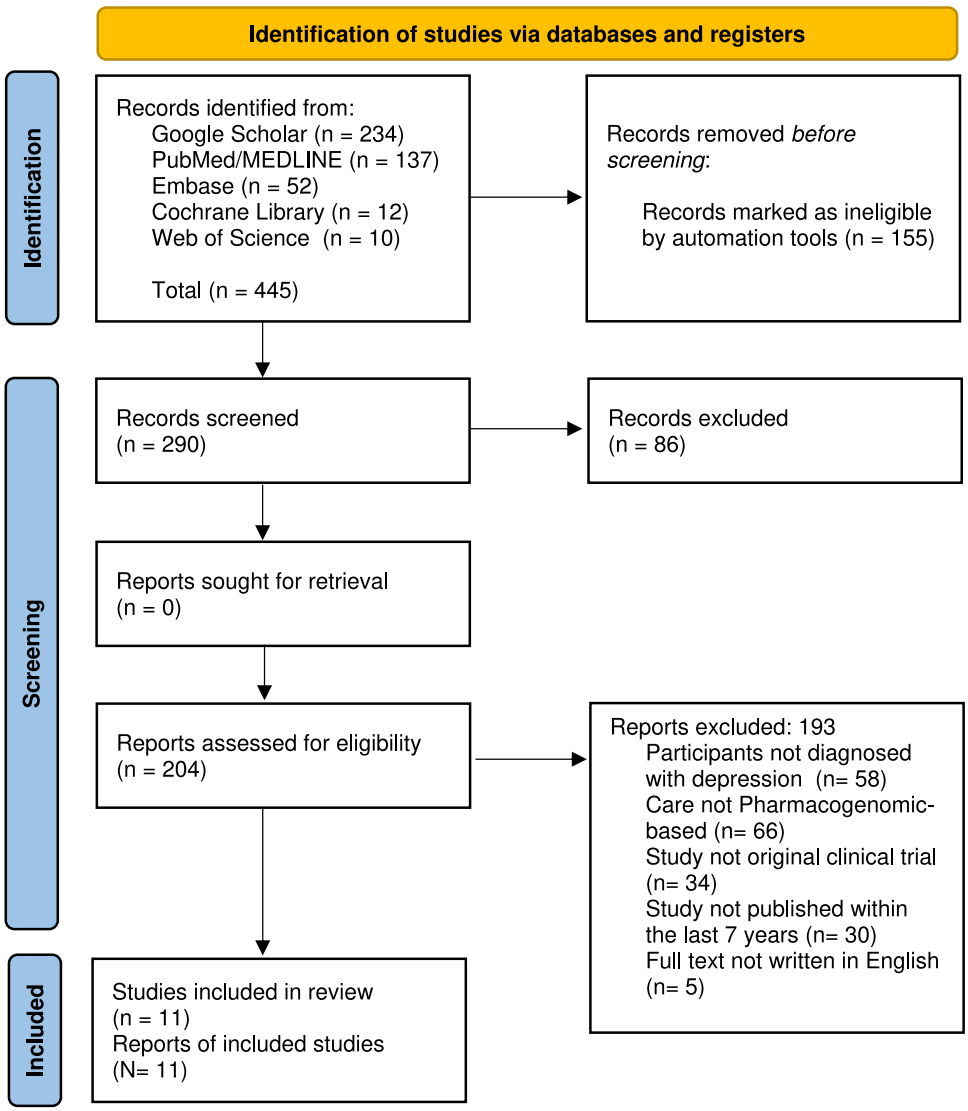

Fig. 1 PRISMA flowchart summarizing the process of selection

3. Data extraction using a standardized template (PRISMA) to ensure consistency and completeness.

Analysis approach

A narrative synthesis was employed to organize and interpret the findings.

Key Analytical Steps

- Categorizing studies by outcomes (e.g., clinical effectiveness, cost-effectiveness, patient satisfaction).
- Identifying trends, gaps, and inconsistencies in the evidence base.
- Assessing the methodological quality of included studies.
- Highlighting evidence on the clinical utility of PGx compared to standard care.

This systematic methodology ensures a comprehensive and critical review of the evidence on the effectiveness of PGx-based care in depression compared to standard care.

To ensure reliability, two reviewers [C.S.O and V.O.A] independently screened articles, extracted data, and resolved discrepancies through consensus with the third reviewer [I.J.O].

Results

Characteristics of included studies

Eleven studies published between 2017 and 2022 were included in this review. All the studies included were randomized controlled trials (RCTs), human studies with sample sizes ranging from 71 to 1,167 subjects, and a cumulative sample size of 4,424. Most studies have compared

the effectiveness of pharmacogenomic-guided treatment for depression using treatment as usual (TAU) as a control [20, 22, 23, 25, 27]. Some studies have employed the Hamilton Depression Rating Scale (HDRS) for the measurement of outcomes [18–21, 24, 26, 27], whereas some have used patient reports [17], the SIGH-D17, the QIDS-SR16, the CCI [6], or the PGxI-I [25]. The duration of follow-up varies between studies and ranges between 8 weeks and 24 weeks. Patients who had been diagnosed with major depressive disorder were the subjects of most studies (17, 18, 20, 21, 23, 24, 27). Forester et al. included elderly subjects aged 65 and above [21], whereas two other studies included subjects younger than 18 [23, 24]. Table 1

Blinding was difficult to achieve in most of the trials as clinicians needed to know how to proceed with PGx-based therapy based on patients' profiles [18, 20, 21, 23, 24, 27]. Common PGx testing was done using various approved methods (e.g., Pillcheck), which detects variations in patients' genetic profiles and provides detailed clinical recommendations in tandem with already existing guidelines [18].

Clinical outcomes: response and remission rates

Generally, there were better reported outcomes for PGx-guided treatment and the usual treatment for depression in improving symptoms [17–27]. However, recent studies have reported the superiority of PGx-guided treatment in achieving response and remission. [18, 20, 21, 26, 27]. Papastergio et al. reported improvement in the symptoms of depression in patients treated with PGx-guided treatment compared with those who received standard treatment [1]. Han et al. found statistically significant differences between the group treated with usual treatment and the PGx-based antidepressant treatment (PGxATx) group p=0.01, also with significant variations between remission scores [27]. Using the Hamilton Rating Scale for depression, PGx-guided treatment was found to be superior to treatment as usual (TAU) in achieving both response and remission [18–20, 24, 26]. Duration of follow-up does not significantly impact clinical outcomes, and the response and remission rates achieved at 8 weeks do not significantly differ from those achieved at 12 and 24 weeks [21, 23, 25–27]. Vande Vort et al., in a study amongst 176 U.S.-based adolescents aged 13–18 years, reported no statistically significant differences between the two groups both at 8 weeks and 6 months, although the TAU group was prescribed higher doses of SSRIs [23].

Overall, adverse reactions were found to be lower in PGx-guided treatment [20, 22, 25]. Although the study by Perlis et al. found no significant differences in the outcomes of comorbidities between the treatment groups [22], most of the studies reported decreases in disability scales in the PGx groups [21, 22, 24]. Green et al. also reported improved satisfactory patient scores [18].

Cost-effectiveness of PGx-based depression care

The findings of the included studies on the effectiveness of PGx-based care indicate that it is cost-effective to reserve PGx-based care for patients who are resistant to standard care [18]. As there is no significant difference in the improvement of symptoms between PGx-based treatment and usual treatment, this reduces the cost-effectiveness of pharmacogenomics-guided treatment as the first-line treatment for depression. However, its superiority in achieving response and remission makes it a cost-effective means of managing intractable depression.

Heterogeneity of findings across studies

The findings across the included studies are relatively uniform, with differences in sample size, duration of follow-up, and outcome measures. Also, the studies employed different population groups ranging from adolescents to adults aged >65 years [18, 21, 23]. Across studies, analysis of results was mostly done as intended to treat, although Greden et al. analyzed as treated [18]. The heterogeneity across the studies was not significant enough to warrant subgroup analysis.

Discussion

The introduction of PGx, which promises to modify pharmaceutical selection based on a patient's genetic profile (precision-treatment strategy), has increased the emphasis on an individualized approach to depression treatment. This review of current evidence examines the effectiveness of PGx-guided care in addressing depression as compared to standard care. The findings across included studies show mixed results regarding the effectiveness of PGx testing in treating depression when compared to traditional management. Some studies, especially Papastergiou et al. (2021) [17] and Thase et al. (2019) [20], discovered that PGx-guided treatment resulted in considerable increases in response and remission rates, especially in patients who had previously failed to experience remarkable outcomes with multiple antidepressant medications at week 8 of follow-up. However, other trials did not report substantial differences in symptom improvement between PGx-guided care and standard treatment as usual (TAU) at week 8 [18, 19, 21–27]. Although most studies (8) reported that significant improvements

Table 1 Overview of included studies

Author & Year	Study Design	Sample Size & Patient Characteristics	Outcomes	Efficacy	Conclusion
Papastergiou et al., 2021[17]	Randomized Controlled Trial	A total of 213 outpatients diagnosed with major depressive disorder (MDD) and/or generalized anxiety disorder were randomly assigned to receive either pharmacogenomics-guided treatment (n = 105) or standard antidepressant treatment (n = 108). The participants were blinded to the study.	The primary outcome is depression while the secondary outcomes are generalized anxiety and disability. Patient-reported outcomes of depression, anxiety, disability, and treatment satisfaction were evaluated at months 0, 1, 3, and 6	Compared to patients who received standard treatment, pharmacogenomics-guided treatment participants showed greater improvement in the primary and secondary outcomes. Both groups showed similar improvement in Treatment satisfaction.	Pharmacogenomic testing may be a valuable tool to allow pharmacists to collaborate more effectively in enhancing clinical treatment decisions
Greden et al., 2019 [18]	A large, patient- and rater-blinded, randomized, controlled study	Outpatients (N = 1167) diagnosed with MDD and have had inadequate response to at least one antidepressant	Primary outcome was improvement in symptom (change in HAM-D17) at week 8. Secondary outcomes included response (≥50% decrease in HAM-D17) and remission (HAM-D17 ≤ 7) at week 8	At week 8, there was no significant statistical difference in symptom improvement between the pharmacogenomic-guided care group and TAU (27.2% versus 24.4%, p = 0.107). However, improvements in response (26.0% versus 19.9%, p = 0.013) and remission (15.3% versus 10.1%, p = 0.007) were statistically significant	Although Pharmacogenomic testing did not significantly improve symptoms over the 8-week period, response and remission rates for difficult-to-treat depression patients were significantly improved over standard of care.
Shan et al., 2019 [19]	A Randomized Single-Blind Study. In the guided group, the treating physician received a pharmacogenomic-based report to guide medication selection, and patients were informed their treatment was influenced by DNA testing. In contrast, the unguided group received treatment based solely on the physician's clinical judgment, without pharmacogenomic input.	71 patients with depression were randomized into PGx-guided (N = 31) and unguided (N = 40) groups, respectively	The HAMD-17 (Hamilton Rating Scale for Depression), the Hamilton anxiety scale, and treatment emergent symptom scale were used to evaluate the clinical efficacy and side effects at baseline and after 2, 4, and 8 weeks of treatment	No significant difference ($P > 0.05$) in HAMD-17 total scores, response and remission rates was found between the guided and unguided groups at the end of the treatment. However, the response and remission rates of the guided group were numerically higher than the unguided group: 74.19% vs 57.5%; 61.29% vs 45.0% respectively.	This study suggested that pharmacogenomic testing might not significantly enhance the clinical efficiency and safety for the guided group.

Table 1 (continued)

Author & Year	Study Design	Sample Size & Patient Characteristics	Outcomes	Efficacy	Conclusion
Thase et al., 2019 [20]	Randomized Controlled Trial	912 Participants diagnosed with MDD who did not have an adequate response to at least 1 psychotropic medication in the current episode of MDD. Patients were randomized to either the treatment as usual (TAU) or the guided-care arm	Symptom improvement, response, and remission were assessed using the Hamilton Depression Rating Scale (HDRS-17)	For participants on medications affected by gene-drug interactions, outcomes at week 8 were significantly better in the guided-care group compared to the treatment as usual (TAU) group: symptom improvement was 27.1% vs. 22.1% (P = .029), response was 27.0% vs. 19.0% (P = .008), and remission was 18.2% vs. 10.7% (P = .003). In patients who switched medications, the guided-care group also showed significantly better results across all outcomes compared to TAU (P = .011 for symptom improvement, P = .011 for response, P = .008 for remission).	The adoption of a combinatorial pharmacogenomic test greatly improved outcomes for individuals with Major Depressive Disorder (MDD) who had experienced at least one medication failure. This improvement was achieved by identifying patients with expected gene-drug interactions and focusing treatment on them.
Forester et al., 2020 [21]	Post hoc data analysis from a blinded, randomized controlled trial comparing two active treatment arms.	The study included 206 adults who were 65 years of age or older at baseline, and had been diagnosed with MDD. Additionally, study participants are those who have not responded well to at least one medication during their current depressive episode.	The mean percentage of symptom improvement, response rate, and remission rate at week 8 were assessed using the 17-item Hamilton Depression Rating Scale, along with medication switching and comorbidity moderator analysis.	At week eight, there was no significant difference in symptom improvement between guided care and TAU. Compared to TAU, guided care had a noticeably better response and remission. Results in the guided-care group continued to improve consistently until the completion of the 24-week open-design trial, demonstrating the durability of the effect.	Combinatorial pharmacogenomic test-guided medication selection improved outcomes over TAU among older adults with depression

Table 1 (continued)

Author & Year	Study Design	Sample Size & Patient Characteristics	Outcomes	Efficacy	Conclusion
Perlis et al., 2020 [22]	Randomized, controlled, participant- and rater-blind trial	Participants consisted of 304 outpatients with nonpsychotic major depressive disorder randomized 1:1 to assay-guided treatment (AGT; N = 151) or treatment-as-usual (TAU; N = 153)	Change from Baseline in SIGH-D-17 was the primary outcome. The secondary outcomes were changes in Quick Inventory of Depressive Symptomatology (QIDS-SR16), and Clinical Global Impression-Improvement (CGI-I) scores. All measures were collected at baseline and weeks 0, 2, 4, 6, and 8	At Week 8, there was no significant difference between AGT and TAU for the primary outcome. According to exploratory analyses, significantly fewer people had their depression symptoms worsen after AGT. Treatment that was in line with the assay results was linked to a higher chance of remission.	Pharmacogenomic testing that assessed both pharmacokinetic and pharmacodynamic variants did not lead to significant improvements in the primary efficacy outcome when providers were not required to follow the test results. However, patients whose treatments closely followed pharmacogenetic evidence-based guidelines were more likely to achieve remission.
Vande Voort et al., 2022 [23]	Randomized Controlled Trial	176 adolescents between the ages of 13 to 18 years with moderate to severe MDD. Randomized to either a pharmacogenetic-guided arm (GENE arm, n = 84) or a treatment-as-usual arm (TAU arm, n = 92).	Symptom improvement, side effects, and satisfaction were assessed throughout the study at 4 weeks, 8 weeks, and 6 months.	There were no differences between the GENE and TAU arms at 8 weeks or 6 months for symptom improvement, side effect burden, or satisfaction. The results of pharmacogenetic testing in this study may have been diluted by patients in the TAU group who were prescribed medications without gene-drug interactions. Pharmacogenetic testing could be particularly valuable for patients who are prescribed medications with significant gene-drug interactions.	Combinatorial pharmacogenetics-guided treatment did not demonstrate improved outcomes compared to TAU in adolescents with MDD.

Table 1 (continued)

Author & Year	Study Design	Sample Size & Patient Characteristics	Outcomes	Efficacy	Conclusion
Tiwari et al., 2022 [24]	3-arm (GEN, EGEN and TAU), Multi-center, Rater-blinded, randomized, controlled trial	276 patients who are ≥18 years and diagnosed with MDD. Additionally, patients had poor response to at least one anti-psychotic drug within the combinatorial pharmacogenomics report for the current episode of depression. Patients who had high risk of suicide, severe psychiatric or cognitive disorders, and serious medical conditions were excluded.	Improvement in symptoms at week 8, using the HAM-D17, was the primary outcome while the secondary outcomes were drug response and remission measured at week 8.	There was no significant difference in the primary endpoint, percent and mean absolute decrease in HAM-D17 score, between the GEN and TAU arms at week 8. However, patients in the pharmacogenomic-guided group had numerically higher outcomes for symptom improvement, response rate and remission rate.	Despite the limitations of this study including small sample size, comparing the effect size with that in [2] shows similar effect sizes indicating that the numerically higher outcomes may represent true differences between the experimental arms. The study concludes that Combinatorial pharmacogenomic testing provides clinicians with key genetic insights to help personalize and improve depression treatment.
Perez et al., 2017 [25]	Randomized, Double-Blind Clinical Trial	316 Patients with a Clinical Global Impression-Severity (CGI-S) score of 4 or higher needing either new antidepressant medication or changes to their current regimen. Patients were randomly assigned to either PGx-guided treatment (n = 155) or standard treatment as usual (TAU, control group, n = 161).	The primary outcome was the proportion of patients who achieved a sustained response denoted as the Patient Global Impression of Improvement (PGI-I ≤ 2) within the 12-week follow-up.	The PGx-guided treatment group showed a greater responder rate at 12 weeks compared to TAU, but there was no difference in maintained response during the trial term (primary endpoint). Patients with one to three failed medication trials experienced more consistent effects. At six weeks and twelve weeks, the PGx-guided group had greater odds than the controls of achieving a better tolerance in subjects who had reported side effect load at baseline.	PGx-guided treatment significantly improved the response of patients with major depressive disorder (MDD) after 12 weeks, especially in those who had failed multiple medications before. However, this improvement did not lead to a sustained response over the period of the trail. Additionally, patients experienced a significant reduction in side effects.

Table 1 (continued)

Author & Year	Study Design	Sample Size & Patient Characteristics	Outcomes	Efficacy	Conclusion
Bradley et al., 2018 [26]	A randomized clinical trial	685 patients diagnosed with depression or as well as comorbid patients displaying both depression and anxiety	Baseline patient assessments were conducted using the HAM-D17 and the Hamilton Rating Scale for Anxiety (HAM-A), with follow-up data collected at 4, 8, and 12 weeks after the initial baseline.	In patients diagnosed with depression, response and remission rates were significantly higher in the pharmacogenetics-guided group compared to the control group at the 12-week mark. Additionally, patients in the pharmacogenetics-guided group with anxiety showed notable improvement in HAM-A scores at both 8 and 12 weeks, along with higher response rates. However, no significant improvement was observed in patients with mild depression.	Pharmacogenetic-guided medication selection greatly improves the prognosis of patients with anxiety or depression diagnoses.
Han et al., 2018 [27]	8-week, Randomized, Single-blinded Clinical Trial	100 patients with MDD were recruited and randomly assigned either to Pharmacogenomic-based antidepressant treatment (PGATx) (n=52) or TAU (n=48) groups	A change in the HAMD-17 total score from the baseline to the end of treatment was the primary outcome. Investigations were also conducted into response rate, remission rate, and the change in the overall score of the frequency, intensity, and burden of side effect ratings (FIBSER) from the start to the end of treatment.	The mean change in the HAMD-17 score between the two groups showed a significant difference, with PGATx having a −4.1 point advantage by the end of treatment. Similarly, the mean change in the FIBSER score from baseline was significantly different, with PGATx showing a −2.5 point benefit. Response rates were also significantly higher in the PGATx group compared to the TAU group at the end of treatment, while remission rates were numerically higher in the PGATx group, though the difference was not statistically significant.	This clearly reveals that in terms of efficacy and tolerability, PGATx may be a preferable therapy choice for MDD.

in response and remission rates were observed in patients whose treatments were guided by PGx testing, highlighting the promising potential of this approach to improve personalized care for depression [17, 18, 20, 21, 24–27]. Targeting gene-drug interactions appears to be critical in the efficacy of PGx-based therapeutic approaches.

In these studies comparing PGx-guided care to traditional therapies, the overall findings indicate that, while symptom relief may not always be statistically different, the impact on treatment response and remission is greater among PGx-guided groups. These et al. (2019) [20] revealed that individuals with MDD who had failed at least one antidepressant and were subsequently treated with drugs tailored to their genetic profiles had considerably higher responses and remission rates than those who only received standard treatments. These findings highlight the clinical utility of PGx testing, particularly in individuals with gene-drug interactions, among whom traditional therapy techniques may have been less beneficial. When comparing PGx-guided care to typical pharmacological therapies, there are clear advantages for PGx testing. Standard care frequently entails a trial-and-error approach to selecting antidepressants, which can extend the time to remission and expose patients to avoidable side effects. In contrast, PGx-guided treatment seeks to bypass or simplify this trial-and-error process by identifying drugs compatible with the patient's genetic profile, with a particular emphasis on genes implicated in drug metabolism (pharmacokinetics) and drug response (pharmacodynamics). For example, Greden et al. (2019) [18] discovered that patients with gene-drug interactions who received PGx-guided therapy had greater remission rates than those on standard treatment, implying that PGx testing can assist in preventing ineffective treatments while also lessening the risk and burden of side effects.

The safety profile of PGx-guided treatment is generally positive since it allows for more informed drug selection, lowering the risk of adverse drug reactions caused by genetic incompatibilities. Han et al. (2018) [27] found that patients receiving PGx-guided antidepressant medication experienced fewer side effects and improved their depression ratings more than those getting standard treatment. This illustrates the value of PGx testing not only in increasing treatment efficacy but also in improving antidepressant acceptability by avoiding medications that are poorly metabolized or have a higher risk of side effects for certain patients, reinforcing its precision strategy. However, some challenges remain around this precision treatment. Pestril et al. (2021) [22] stated in their study that one of the most difficult challenges in this precision treatment is determining which populations will benefit the most. The study stated this is due to several genetic variations that alter blood levels. The prevalence of several of these variants varies with ancestry, implying that drug efficacy may change between populations. Another significant obstacle is the duration of the trial; it does not evaluate the possibility of longer-term advantages linked to PGx testing. Most published studies only disclose findings for a limited period, mostly not more than 12 weeks [22]. Extensive research may be necessary to fully understand the long-term effects of PGx testing, especially for psychological conditions like depression where the disease's recurring expenses are often associated with worse overall clinical outcomes.

Limitations of PGx testing in psychiatric care

Despite its prospects, several limitations have been identified with PGx testing. While the evidence relating patients' response to antidepressant with genetic variations is still evolving, non-genetic factors, such as environment and comorbidities, also influence treatment outcomes. Additionally, there remains significant variability in recommendations on this approach inasmuch as large-scale trials have shown only modest improvements in response and remission rates. The lack of standardization across commercial PGx testing panels results also contribute to this variability.

Particularly in low-resource settings, the major hurdles are due the poor access to the widespread use and clinical acceptance of PGx testing. This significant hurdle is the economic expense of genetic testing and the infrastructure required to support its real-world implementation in clinical practice [28]. Despite lowering with time, the cost of PGx tests may still be prohibitively expensive in contexts where healthcare financing and insurance are limited. Furthermore, technological difficulties in low-resource settings, such as the lack of access to advanced genetic testing facilities and the required software for interpreting results, thereby impeding the implementation of PGx-guided care. Beyond economic and technological limitations, societal and educational obstacles contribute to the sluggish adoption of PGx testing. Many regions have low awareness of the benefits of genetic testing among healthcare professionals and patients.

Furthermore, legislative and policy constraints must be overcome. Many healthcare systems need clear criteria or reimbursement procedures for PGx testing, making it challenging for clinicians to provide these services as part of their standard care. As a result, legislative policies that make it easier to include PGx in routine care protocols will be critical for its widespread use, particularly among impoverished groups.

In summary, PGx-guided care is a promising addition to the treatment of depression, with the potential to improve treatment results, particularly for patients who have not responded well to standard therapies, especially medications. PGx approach, which tailors antidepressant selection based on genetic profiles, can increase both efficacy and

safety, reducing the need for the trial-and-error method commonly involved with antidepressant therapy. To fully realize the benefits of PGx testing, various economic, technological, and regulatory barriers must be overcome, particularly in low-resource areas. More research is needed to investigate the long-term effects of PGx-guided therapy and establish the best way to adopt this promising method worldwide.

Future perspective

Pharmacogenomics service delivery includes improving the population's health, increasing access to care, and reducing costs [29]. For PGx testing in depression to become mainstream, stakeholders must be ready to address all three aspects, especially the latter as regards cost. Individuals suffering from depressive symptoms often report difficulty in accessing care due to various factors such as work responsibilities, lack of access to appropriate means of transportation, or lack of trust in the medical personnel [30]. With PGx testing, although we intend to optimize treatment through precision medicine, future clinical trials should ensure that hospital waiting times are reduced to the minimum and that test results are also conveyed positively. Studies with moderate to long-term follow-up periods should plan effective strategies for reducing the attrition rates of participants. Even though the systematic review by Cheng et al. reported a holistic meta-analytic result of the effectiveness of pharmacogenomics on the response and remission of treatment-resistant depression and found no statistically significant differences between the effect sizes for acceptability and side effects between PGx-based care and treatment as usual, more reviews and meta-analyses are required to increase the quality of evidence available of the use of PGx in depression management [31].

Many research gaps remain in CYP2D6 allelic variability across races, especially in African and Middle Eastern Populations [32–34]. Since the CYP2D6 gene plays a significant role in metabolism, it would be interesting to see results from more clinical trials in these regions. Finally, as pharmacogenomics continues to evolve, it will play an increasingly prominent role in the future management of not only depression but multiple mental health disorders, making treatments more tailored, acceptable, and efficient across various fields of medicine.

Conclusions

The existing evidence suggests that PGx-based care demonstrates superior efficacy in depression treatment compared to standard care, particularly for patients who have not found relief through standard care. While studies present mixed results—some indicating a notable increase in response and remission rates with PGx-guided treatment, particularly in treatment-resistant cases—others show little difference compared to traditional methods. This inconsistency signals a need for further research to clarify the contexts in which PGx testing can be most beneficial.

As the focus shifts towards personalized medicine, PGx-based care is poised to revolutionize depression management as it anchors on individual genetic profiles. This will minimize the trial-and-error process that often characterizes antidepressant therapy. Enhanced efficacy and reduced side effects can improve patient satisfaction and safety, reinforcing the rationale for its integration into clinical practice. However, economic constraints, technological access in low-resource settings, and a lack of awareness among healthcare providers and patients regarding the benefits of genetic testing are major barriers that persist.

Future efforts must focus on creating cost-effective solutions, enhancing technological infrastructure, and increasing awareness to ensure that all patients can access the benefits of pharmacogenomic-guided therapy. Further studies are needed to thoroughly investigate the long-term effects of PGx-based care and its generalizability to diverse patient populations. For PGx testing to become a mainstream approach, a concerted effort across multiple fronts is necessary—improving health outcomes, increasing accessibility, and, most importantly, making the cost of treatment manageable for all.

Abbreviations DSM: Diagnostic and Statistical Manual of Mental Disorders; 5-HT: Serotonin; DA: Dopamine; MAOIs: Monoamine Oxidase Inhibitors; NE: Norepinephrine; PGx: Pharmacogenomics; SLC6A4: Solute Carrier Family 6 Member 4 (Serotonin Transporter Gene); SSRI: Selective Serotonin Reuptake Inhibitor; 5-HTTLPR: Serotonin-Transporter-Linked Polymorphic Region; MDD: Major Depressive Disorder

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