Curr Treat Options Psych (2024) 11:123–140
DOI 10.1007/s40501-024-00316-x

Hot Topic

Pharmacogenomic Testing to Guide Treatment of Major Depressive Disorder: A Systematic Review

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Published online: 31 May 2024

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s40501-024-00316-x.

Keywords Pharmacogenomics · Pharmacogenetics · Pharmacogenetic testing · Antidepressive agents · Depressive disorder · Depression

Abstract

Purpose of review Major depressive disorder is a prevalent psychiatric illness associated with significant morbidity, mortality, and economic burden worldwide. Despite the widespread use of antidepressants, remission rates among those treated with antidepressants remain low. Opportunities to personalize medication choices and doses and optimize clinical outcomes using pharmacogenomic testing have been evaluated.

Recent findings Several prospective clinical trials and a recent meta-analysis have evaluated the impact of PGx-guided prescribing compared to treatment as usual and found no difference in clinical outcomes for patients with MDD.

Summary We performed a systematic review of all prospective trials evaluating the effect of pharmacogenomic-guided prescribing on clinical outcomes of patients being treated with antidepressants for major depressive disorder. A literature search was performed using PubMed, Scopus, Web of Science, and PsychINFO databases for articles in English published from January 2010 to December 2022. Studies that did not report any patient-level

outcomes were excluded. A total of 2489 studies were screened for eligibility. Full-text screening for 315 yielded 293 exclusions; thus, 22 studies were included. Sixteen of the 22 studies were randomized-controlled trials with durations varying from 90 days to 52 weeks. The findings of this systematic review suggest widespread routine pharmacogenomic testing may not yield significant changes in clinical outcomes when compared to treatment as usual. These results may or may not be generalizable to all persons taking antidepressants given guideline recommendations for pharmacogenomic-guided prescribing in patients on specific antidepressants. Future studies are warranted evaluating the utility of such testing in these subpopulations.

Introduction

Major depressive disorder (MDD) is a psychiatric illness associated with high levels of morbidity that increase economic burden. Between the years of 2010–2018, the economic burden of MDD was estimated to be 326.2 billion dollars in the USA, a 37.9% increase from the 2010 estimation [1]. According to the World Health Organization (WHO), an estimated 5% of the world's adult population suffer from depression [2]. Nonpharmacologic approaches to treating MDD include psychotherapy, transcranial magnetic stimulation (TMS), and electroconvulsive therapy (ECT). While all antidepressants used to treat MDD exhibit similar efficacy, first-line pharmacologic options such as selective serotonin reuptake inhibitors (SSRIs) or selective serotonin and norepinephrine reuptake inhibitors (SNRIs) are often preferred due to their tolerability profile. Other antidepressant subclasses such as atypical antidepressants and tricyclic antidepressants (TCAs) may be prescribed as monotherapy or adjunct to SSRIs or SNRIs to manage MDD. Antidepressants exhibit modest efficacy when treating MDD. Remission rates of MDD symptomatology after first-time trial are estimated at 30%, with subsequent medication trial failures producing lower remission rates [3, 4]. Because remission rates remain low, alternative treatment approaches are always being explored to improve the quality of patient care. One alternative treatment approach that has gained traction over the past decade is moving towards personalized medicine, also referred to as pharmacogenomic-guided prescribing.

Pharmacogenomic-guided prescribing has the potential to improve outcomes mainly through assistance with identifying genetic variants that alter metabolism. In these scenarios, the identification of polymorphisms can better assist prescribers with dosing these medications to avoid adverse effects and optimize efficacy. Specifically, patients with polymorphisms of CYP2C19, CYP2D6, and CYP2B6 may benefit from pharmacogenomic (PGx) testing prior to antidepressant prescribing [5•]. The Clinical Pharmacogenetics Implementation Consortium (CPIC), Food and Drug Administration (FDA), and the International Society of Psychiatric Genetics (ISPG) recommend pharmacogenomic testing and personalized dosing for antidepressants metabolized by certain CYP enzymes. The dosing recommendations reflect interindividual differences in pharmacokinetic parameters in those with these genetic variants of CYP enzymes such as CYP2C19 and CYP2D6. There is also evidence that certain genes and alleles such as SLC6A4 and HTR2A may influence clinical response to certain antidepressants; existing data does not support their screening for these genes or alleles to inform antidepressant prescribing [5•].

Currently, routine pharmacogenomic testing in psychiatry and specifically for patients initiated on antidepressants is not recommended for several reasons. Access to testing is difficult and expensive, prescribers often report that interpretation can be futile due to clinician unfamiliarity with PGx testing and lack of knowledge about the evidence of PGx use in psychiatry, and incorporation of testing into current workflows is challenging [6]. Additionally, there is little evidence demonstrating improved clinical outcomes in patients receiving PGx-guided prescribing. Several prospective clinical trials have evaluated the impact

of PGx-guided prescribing compared to treatment as usual and found no difference in clinical outcomes for patients with MDD. However, in recent years, additional randomized controlled trials have been conducted to add to the body of literature regarding PGx-informed pharmacotherapy in psychiatry. The purpose of this systematic review is to evaluate available prospective literature and determine the impact of PGx-guided prescribing on clinical outcomes such as rating scale changes, response, and remission in patients who received antidepressant treatment for MDD.

Methods

The systematic review protocol was registered with PROSPERO, an international registry of systematic reviews. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to conduct this review.

Search Strategy

A literature search was performed using PubMed, Scopus, Web of Science, and PsychINFO databases for articles in English published between January 2010 to December 2022. Literature search strategies were developed in collaboration with a research librarian. The following search terms were utilized: pharmacogenomics and depression. MeSH terms, index terms, and subject headings were included where available. The synonyms of the search terms can be found in Table 1. The date of the last search of databases specified above was January 27, 2023.

Eligibility Criteria

Studies included were published in a peer-reviewed journal, were prospective trials assessing the clinical utility of Pgx testing to inform pharmacotherapy treatment decisions for major depressive disorder, and reported clinical outcomes for either efficacy or safety. Included in the study were adults ≥ 18 years of age treated with an antidepressant from drug classes with MDD indications: selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase

Table 1. Search terms and synonyms

Search term	Synonyms
Pharmacogenomic	Pharmacogenetic, "pharmacogenetics" [MeSH]
Depression	Major depressive disorder, MDD, antidepres*, "disorder, major depressive" [MeSH], "agents, antidepressant" [MeSH]

inhibitors, and atypical antidepressants (mirtazapine, trazodone, bupropion, combination olanzapine/fluoxetine). Studies that did not report any patient-level outcomes were excluded. Articles also excluded were pharmacokinetic studies, pediatric studies with patients < 18 years of age, retrospective studies, genome-wide association studies, pharmacoeconomic analyses, reviews, systematic reviews, meta-analyses, letters, book chapters, case studies, case reports, editorials, commentaries, discussion papers, and conference proceedings.

Study Screening

The study team used Covidence, a web-based collaboration software platform that streamlines the production of systematic and other literature reviews, for study screening, data extraction, and quality assessment. Two study team members completed title and abstract screening independently for each article to determine eligibility for inclusion. Each study team member independently designated an inclusion decision for each article as either "yes," "no," or "maybe." Articles with "yes" or "maybe" designations were screened via full-text assessment to determine eligibility for data extraction. The study team discussed and came to a consensus for articles with conflicting designations that needed to be resolved.

Data Extraction and Synthesis

Independent data extraction was performed by four members of the study team using a standardized data extraction form created in Covidence Extraction and checked by one author. The following data were extracted: (1) study information (study design, intervention, follow-up period, primary objectives, statistical methods); (2) population (setting, subject eligibility criteria); (3) patient baseline characteristics; (4) outcomes. For data synthesis, thematic analysis was conducted (refer to supplemental Table 1: sample data extraction template).

Quality Assessment

Two authors independently conducted quality assessments of all included studies using the Cochrane Risk of Bias tool [7] to evaluate for selection bias, reporting bias, performance bias, detection bias, attrition bias, and other biases in the following seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. For each domain, the authors assessed the study and assigned a designation of high, low, or unclear risk of bias for that item. For domains with inconsistent ratings, the authors then discussed the studies to come to a consensus.

Results

The systematic review process is summarized in Fig. 1. A total of 2489 studies were screened for eligibility. Full-text screening for 315 yielded 293 exclusions. The most common reason for exclusion was "wrong study design." Once all screening was completed, 22 studies remained and were included in the analysis. Characteristics of the 22 studies are listed in Table 2. Six of the included studies were prospective cohort trials [8–13]; four of these studies did not include a control arm and only evaluated PGx-guided treatment [10–13]. The rest were randomized-controlled trials. Studies included sample sizes ranging from 44 to 1944; four studies had sample size < 100, 14

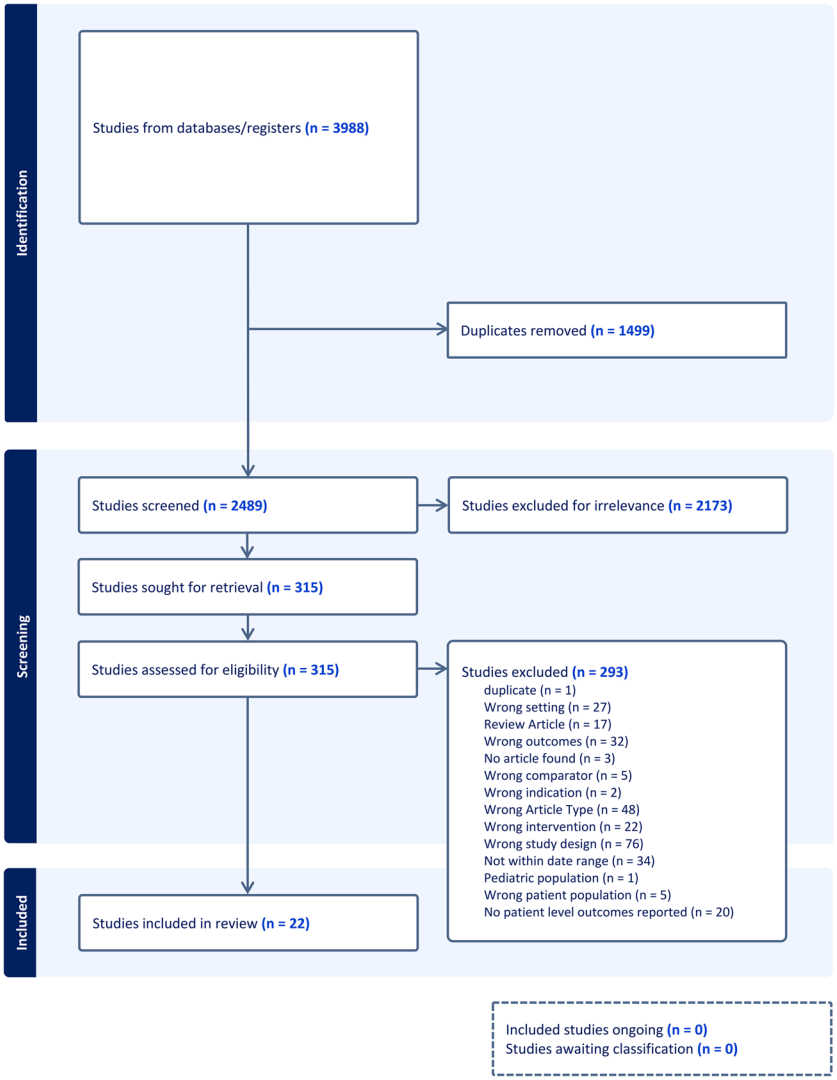

Fig. 1 Systematic review process

Table 2. Summary of retrieved literature [8–22, 23•, 24–30]

Author/year	Trial design	Sample size	Diagnosis/population	Intervention	Relevant outcome(s)	Findings (guided vs. unguided treatment)	Study duration
Prospective cohort studies							
Hall-Flavin 2012 [8]	Prospective cohort study	44	Primary diagnosis of MDD HAMD-17 ≥ 14 Outpatients, 55% women, mean age 42, QIDS-C16 baseline 16	PGx-guided treatment versus unguided treatment	Change in HAMD-17, QIDS-C16	HAMD-17: −30.8% (PGx) vs −18.2% (TAU), $p = 0.002$ QIDS-C16: −31.2% (PGx) vs −7.2% (TAU), $p = 0.002$	8 weeks
Hall-Flavin 2013 [9]	Prospective cohort study	227	Primary diagnosis of MDD HAMD-17 ≥ 14 Outpatients, 73% women, mean age 43, baseline HAMD-17 23	PGx-guided treatment versus unguided treatment	Change in HAMD-17, QIDS-C16, and PHQ-9 scores,	HAMD-17: −46.9% (PGx) vs −29.9% (TAU), $p < 0.0001$ QIDS-C16: −44.8% (PGx) vs −26.4% (TAU), $p < 0.0001$	8 weeks
Brennan 2015 [10]	Naturalistic, prospective cohort study	625	Primary diagnosis of MDD or anxiety 43% MDD diagnosis, 17% bipolar disorder diagnosis, 66% women, 88% white, mean age 41, baseline QIDS-SR16 11.6	Pgx-guided treatment	Change in QIDS-SR16	QIDS-SR16: −7.8 ($p < 0.001$)	12 weeks
Torrellas 2017 [11]	Prospective cohort study	291	Any psychopathology compatible with mental or behavioral disorders, HDRS ≥ 8, outpatients, 51% women, mean age 44	PGx-guided treatment	Remission rate	HDRS remission: 29.2%	12 weeks
Tanner 2018 [12]	Naturalistic, open-label, prospective study	1871	Moderate-severe depression, baseline BDI ≥ 20, outpatients, 70% women, mean age 41, baseline BDI 34	PGx-guided treatment	Change in BDI, response, and remission rate	BDI: −27.9% BDI response: 25.7%, BDI remission: 15.2%	12 weeks

Table 2. (continued)

Author/year	Trial design	Sample size	Diagnosis/population	Intervention	Relevant outcome(s)	Findings (guided vs. unguided treatment)	Study duration
Wood 2022 [13]	Naturalistic, open-label, prospective study	53	Outpatient veterans with polypharmacy and 2 or more mental health medications, 52.8% MDD, 64.1% PTSD, 67% white, 66% men, mean age 52	PGx-guided treatment	Change in PHQ-9 at week 12, change in the number of psychiatric medications prescribed	PHQ-9: −2.14 No change in overall psychiatric medications prescribed	12 weeks
Randomized-controlled trials							
Winner 2013 [24]	Randomized-controlled trial	51	Primary diagnosis of MDD HAMD-17 ≥ 14 Outpatients, 81% women, 98% white, mean age 49	PGx-guided treatment versus unguided treatment	Change in HAMD-17, QIDS-C16, and PHQ-9 scores, response and remission rate	HAMD-17: −30.8% (PGx) vs −20.7% (TAU), $p = 0.28$ QIDS-C16: −27.6% (PGx) vs −22.1% (TAU), p = NS PHQ-9: −35.4% (PGx) vs −21.3% (TAU), $p = 0.18$ HAMD-17 response: 36% (PGx) vs 20.8% (TAU), OR = 2.14; 95% CI: 0.59–7.69 HAMD-17 remission: 20% (PGx) vs 8.3% (TAU), OR = 2.75; 95% CI: 0.48–15.80	10 weeks

Table 2. (continued)

Author/year	Trial design	Sample size	Diagnosis/population	Intervention	Relevant outcome(s)	Findings (guided vs. unguided treatment)	Study duration
Singh 2016 [21]	Randomized-controlled trial	152	Primary diagnosis of MDD, HDRS≥18 60% women, mean age 44, baseline HDRS 25	PGx-guided treatment versus unguided treatment	Remission rate	HDRS remission: 72% (PGx vs 28% (TAU)), RR=2.52 (95% CI 1.71–3.73, $p<0.0001$ RR=2.52 (95% CI=1.71–3.73, $z=4.660$, $p<0.0001$)	12 weeks
Stamm 2016 [14]	Randomized-controlled trial	298	Primary diagnosis of MDD, HDRS-21≥15 Inpatients, 62% severe depression, 63% women, mean age 43, baseline HDRS 25	FKBP5 rs1360780 variant genotyping in both algorithm-based treatment group versus treatment as usual	Remission rate	FKBP5 variants TT 69.6% vs CT/C/C 53.5%, p=NS	14 weeks
Olson 2017 [16]	Randomized-controlled trial	237	Diagnosis of any neuropsychiatric disorder Outpatients, 60% MDD, 68% women, mean age 41	PGx-guided treatment versus unguided treatment	Hospitalization rate, adverse effect rate	Hospitalization: 10% (PGx and TAU), p=NS At least 1 adverse effect reported: 28% (PGx) vs 53% (TAU), p=0.001	90 days
Perez 2017 [30]	Randomized-controlled trial	361	Primary diagnosis of MDD, Inpatients/outpatients, 64% women, 92% white, mean age 51, baseline HDRS-17 19	PGx-guided treatment versus unguided treatment	Proportion of patients achieving a sustained response (PGI-I≤2)	PGI response: 38.5% (PGx) vs 34.4% (TAU), p=0.48 OR 1.19; 95% CI: 0.74–1.92, p=NS)	12 weeks

Table 2. (continued)

Author/year	Trial design	Sample size	Diagnosis/population	Intervention	Relevant outcome(s)	Findings (guided vs. unguided treatment)	Study duration
Bradley 2018 [18]	Randomized-controlled trial	685	DSM-V diagnosis of MDD or an anxiety disorder, 73% women, mean age 47, 63% white, baseline HAMD-17 20	PGx-guided treatment versus unguided treatment	Response and remission rate	HAMD-17 response: OR: 4.72; 95% CI; 1.93–11.52, $p=0.001$ HAMD-17 remission: OR: 3.54; 95% CI; 1.27–9.88, $p=0.02$	12 weeks
Han 2018 [19]	Randomized-controlled trial	100	DSM-V diagnosis of MDD, 100% Korean patients, 38% women, mean age 44, baseline HAMD-17 24	PGx-guided treatment versus unguided treatment	Change in HAMD-17, response, and remission rate	HAMD-17: −16.1 (PGx) vs −12.1 (TAU), $p=0.036$ HAMD-17 response: 71.7% (PGx) vs 43.6% (TAU), $p=0.014$ HAMD-17 remission: 45.5% (PGx) vs 25.6% (TAU), $p=0.07$	8 weeks
Greden 2019 [20]	Randomized-controlled trial	1167	Diagnosis of MDD, QIDS-SR16/QIDS-C16≥11, 71% women, mean age 48, 81% white, baseline HAMD-17 21	PGx-guided treatment versus unguided treatment	Change in HAMD-17, response, and remission rate	HAMD-17: −27.2% (PGx) vs −24.4% (TAU), $p=$NS HAMD-17 response: 26.6% (PGx) vs 19.9% (TAU), $p=0.007$ HAMD-17 remission: 15.3% (PGx) vs 10.1% (TAU), $p=0.007$	8 weeks

Table 2. (continued)

Author/year	Trial design	Sample size	Diagnosis/population	Intervention	Relevant outcome(s)	Findings (guided vs. unguided treatment)	Study duration
Shan 2019 [26]	Randomized-controlled trial	71	DSM-V diagnosis of MDD, baseline HAMD-17≥17, 100% Chinese patients, 63% women, mean age 28	PGx-guided treatment versus unguided treatment	Change in HAMD-17, response, and remission rate	HAMD-17: −21 (PGx) vs −20.9 (TAU), $p=0.21$ HAMD-17 response: 60.9% (PGx) vs 52.4% (TAU), $p=0.14$ HAMD-17 remission: 61.3% (PGx) vs 45% (TAU), $p=0.17$	8 weeks
Perlis 2020 [27]	Randomized-controlled trial	304	DSM-V diagnosis of MDD, 72% women, mean age 48, 73% white, baseline HAMD-17 22	PGx-guided treatment versus unguided treatment	Change in HAMD-17, response and remission rate	HAMD-17: −43% (PGx) vs −46% (TAU), $p=0.5$ HAMD-17 response: 40% (PGx) vs 48% (TAU), $p=0.17$ HAMD-17 remission: 24% (PGx) vs 31% (TAU), $p=0.23$	8 weeks
Ruano 2020 [15]	Randomized-controlled trial	1500	Diagnosis of MDD, inpatients, 51% women, 28% aged 21–30, 56.7% white	CYP2D6 genotype-guided treatment versus unguided treatment	LOS, 30-day readmission	LOS: 178.5 h (Pgx) vs 172.6 h (TAU), $p=$NS 30-day readmission:10.1% (PGx) vs 9% (TAU), $p=$NS	Not specified

Table 2. (continued)

Author/year	Trial design	Sample size	Diagnosis/population	Intervention	Relevant outcome(s)	Findings (guided vs. unguided treatment)	Study duration
McCarthy 2021 [17]	Randomized-controlled trial	182	Any psychiatric diagnosis with depression as prominent clinical feature, treatment-resistant depression defined as a past failure with at least 1 previous adequate trial of an antidepressant, 13% bipolar disorder diagnosis, veterans, 24% women, mean age 51, 76% white, baseline QIDS-SR 13	PGx-guided treatment versus unguided treatment	QIDS-SR, remission rate	QIDS-SR16 remission: 29% (PGx) vs 21% (TAU), OR: 1.54; 95% CI; 0.26–1.63, p=NS	8 weeks
Papastergiou 2021 [22]	Randomized-controlled trial	213	Diagnosis of MDD or GAD, outpatient, 75% women, mean age 43, baseline PHQ-9 14	PGx-guided treatment versus unguided treatment	Change in PHQ-9 over time	Overt the study period, PHQ-9 scores declined more in the PGx groups vs TAU, F=2.74, p=0.04	6 months
Bohlen 2022 [28]	Randomized-controlled trial	175	DSM-V diagnosis of MDD, PHQ-9≥10, outpatients, 82% women, mean age 45	PGx-guided treatment starting at week 4 vs week 12	Change in PHQ-9, BDI, QIDS scores	PHQ-9 score: −0.04 (week 4 vs 12), p=0.56 BDI-score: −0.05 (week 4 vs 12), p=0.45 QIDS score: 0.04 (week 4 vs 12), p<0.0001	24 weeks

Table 2. (continued)

Author/year	Trial design	Sample size	Diagnosis/population	Intervention	Relevant outcome(s)	Findings (guided vs. unguided treatment)	Study duration
Oslin 2022 [23•]	Randomized-controlled trial	1944	Diagnosis of MDD, PHQ-9 ≥ 10, outpatients, 26% women, mean age 48, 69% white, baseline PHQ-9 18	Standard-PGx-guided treatment versus unguided treatment	Proportion of prescriptions with drug-gene interaction written in the 30 days after randomization, PHQ-9 change, response and remission rate	Proportion of RX with no drug-gene interaction vs moderate/substantial interaction: OR 4.32; 95% CI; 3.47–5.39, $p < 0.001$ PHQ-9 score: −5.4 (Pgx) vs 4.8 (PGx), p = NS PHQ-9 response: 32.1% (PGx) vs 27.5% (TAU), $p = 0.03$ PHQ-9 remission: 17.2% (PGx) vs 16% (TAU), $p = 0.45$	24 weeks
Tiwari 2022 [29]	Randomized-controlled trial	276	DSM-IV diagnosis of MDD, QIDS-SR16 ≥ 11, 65% women, mean age 41, 84% white, baseline HAMD-17 21	PGx-guided treatment versus enhanced- PGx-guided treatment unguided treatment	Change in HAMD-17 at week 8, response and remission rate	HAMD-17: −27.6% (PGx) vs −22.7% (TAU), $p = 0.27$ HAMD-17 response: 30.3% (PGx) vs 22.7% (TAU), $p = 0.27$ HAMD-17 remission: 15.7% (PGx) vs 8.3% (TAU), $p = 0.131$	52 weeks

HAMD-17/HDRS-17, Hamilton Depression Rating Scale, 17 items; *QIDS-C16*, Quick Inventory of Depressive Symptomatology (Clinician-Rated); *QIDS-SR16*, Quick Inventory of Depressive Symptomatology (Self-Rated); *BDI*, Beck Depression Inventory; *GAD*, Generalized Anxiety Disorder; *PHQ-9*, Patient Health Questionnaire; PGI, Patient Global Impression of Treatment; *LOS*, length of stay; *NS*, non-significant (*p*-values are reported if available on the manuscript)

studies had sample size 100–999, and four studies had sample size of 1000 or greater. Study durations ranged from 90 days to 52 weeks with greater than half of the studies being conducted over 8 or 12 weeks. The genes tested across studies varied; only two studies exclusively evaluated patients with specific variants (FKBP5 rs1360780) or single gene polymorphisms (CYP2D6) [14, 15]. None of the studies limited patients to prescription antidepressants of specific metabolic pathways.

All studies included patients with a primary diagnosis of MDD excluding two, one of which included any neuropsychiatric disorder [16], and the other included patients on 2 or more mental health medications [13]; two studies included patients with a comorbid diagnosis of bipolar disorder [10, 17]. Rating scales used to evaluate depressive symptoms varied among studies and included the 17-item Hamilton Depression Rating Scale (HAMD-17/HDRS-17), the Quick Inventory of Depressive Symptomatology- Clinician-Rated (QIDS-C16), Quick Inventory of Depressive Symptomatology-Self-Rated (QIDS-SR16), the Beck Depression Inventory (BDI), and the Patient Health Questionnaire (PHQ-9). Most studies utilized the HAMD-17/HDRS-17.

Quality assessment of studies using the Cochrane Risk of Bias tool yielded varying results in risk of bias, with seven studies that had a determination of low risk of bias in every domain or at least 6 of 7 domains. Several of the studies were deemed to have higher risk of bias, mostly due to a lack of rater or participant blinding. A full report of quality assessment judgments for each domain can be seen in supplemental Table 2.

Of the 18 studies that compared PGx-guided dosing to treatment as usual, 9 showed a statistically significant difference in at least one primary or secondary clinical outcome, with a greater degree of efficacy in the PGx group. Two of these were prospective cohort studies [8, 9] comparing HAMD-17 and QIDS-C16 reduction; these studies had a higher risk of bias determined by quality assessment review. Seven were randomized controlled trials with low risk of bias, demonstrating differences in HAMD-17 response and remission [18–20], HDRS Remission [21], PHQ9 score reduction [22], PHQ9 response [23•], or adverse effects [16].

Discussion

The findings from this systematic review of 22 prospective studies in patients prescribed antidepressants for MDD suggest that widespread PGx testing does not yield consistently significant changes in clinical outcomes when compared to treatment as usual. Excluding statistically significant changes in depression rating scale scores from a few earlier studies with a weaker trial design, small sample size, and higher levels of bias, more than half of the higher quality and more recent studies do not demonstrate a statistically significant change in depression rating scale scores, response, or remission. Limitations of this systematic review may further impact the generalizability of clinical implications. Prospective studies were not all randomized controlled

trials and clinical outcome measures varied across studies, so data were not pooled for additional analyses.

The largest randomized-controlled trial to date conducted by Oslin and colleagues over a 24-week period evaluated remission rates along with the proportion of prescriptions with a predicted drug-gene interaction written in the 30 days after randomization in those receiving PGx-guided prescribing compared to treatment as usual. Though the difference in remission rates between groups were not statistically significant, those in the PGx-guided prescribing group were less likely to receive a prescription with a drug-gene interaction ($\chi^2 = 169.2$, $p < 0.001$). Further, the estimated risk of prescribing a medication with a moderate or substantial gene interaction was lower in the PGx-guided prescribing group (– 24.6% [95%CI, – 29.5 to – 19.7%, $p < 0.001$] and – 9% [95%CI, – 12.7 to – 5.3%, $p < 0.001$]), respectively. This study did report a significant finding for the secondary outcome of response to treatment, defined as a binary indicator at each time point of at least a 50% decrease from the baseline PHQ-9 score, with PHQ-9 response in 32.1% in the PGx group vs 27.5% in the TAU group ($p = 0.03$) [23•].

A recent systematic review and meta-analysis of prospective, controlled clinical trials, conducted by Brown and colleagues evaluated depressive symptom remission in guided versus unguided antidepressant prescribing for MDD. The pooled relative risk for all included trials was statistically significant at 1.41 (95% CI, 1.15–1.74, $p = 0.001$), indicating a higher likelihood of symptom remission in patients receiving PGx-guided antidepressant prescribing. The authors also noted in their meta-regression analysis that the risk ratio favoring PGx-guided treatment increased based on the number of prior antidepressant treatments (Beta = 0.229, $p = 0.026$) and depressive symptom severity among 12 trials that included this data (Beta = 0.115, $p = 0.036$) [31•].

While these results may initially seem promising, they must be interpreted with caution. The presence of a drug-gene interaction does not guarantee clinical relevance, as the outcomes can vary depending on the specific assay used and the appropriateness of the clinical interpretation of the reports. In the broader context, the integration of routine PGx testing into antidepressant prescribing may not result in significant changes in clinical outcomes. This highlights a major pitfall in existing studies, as the aggregated results based on pooled data evaluating patients on antidepressants with multiple metabolic pathways and different psychiatric comorbidities may not be generalizable to all patients on antidepressants with MDD. This further underscores the importance of conducting future studies to comprehend the limitations in current PGx research for antidepressant prescribing in MDD and to thoughtfully consider the populations to include, keeping in mind the benefit of including an ethnically diverse sample with varying severities of depressive illness. With the exception of two trials conducted in countries in Asia, most studies were not ethnically diverse, and the majority of the samples were from Caucasian patients. Given the interethnic variability in drug metabolism, this becomes relevant when prescribing antidepressants with CYP-mediated metabolism that could be impacted by CYP polymorphisms. Further, of the studies that reported depressive symptom illness severity, most reported mild-to-moderate depressive symptoms and did not report the number of prior antidepressant trials. In light of the possibility that individuals with a higher

number of prior antidepressant trials and more severe depressive symptoms may derive greater advantages from PGx-guided prescribing, and that PGx testing is occasionally pursued in cases of severe or treatment-resistant depressive symptoms following multiple medication trials, it becomes imperative to incorporate these specific patient profiles into clinical trial populations.

The CPIC, FDA, and ISPG all support the use of PGx testing and personalized dosing of antidepressants metabolized by CYP2C19 and CYP2D6 [5•, 32–34]. These recommendations include proposed alternative dosing recommendations based on CYP2C19 and CYP2D6 metabolizer status in patients on selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants [5•, 32, 33]. The Food and Drug Administration (FDA) also makes similar recommendations CYP2C19 and CYP2D6 metabolized medications including venlafaxine and escitalopram [33]. The CPIC and ISPG also endorse routine testing and personalized dosing for those prescribed antidepressants by CYP2B6 such as sertraline and bupropion [5•, 34]. Patients prescribed antidepressants metabolized by these enzymes, especially those with genetic polymorphisms, are likely to yield the greatest benefits from PGx testing per available evidence. These benefits would likely have the greatest impact on poor metabolizers and ultrarapid metabolizers as these designations would yield changes in CYP2C19 or CYP2D6-metabolized antidepressant dosing or selection, potentially yielding better efficacy, tolerability, response, and remission rates.

Conclusion

Widespread, routine PGx-guided prescribing of antidepressants for MDD is less likely to significantly improve clinical outcomes such as depression rating scale scores, response, and remission. However, specific patient populations are more likely to benefit from PGx-guided prescribing. Future studies are warranted evaluating the impact of PGx-guided prescribing of antidepressants in certain subpopulations such as patients with treatment-refractory MDD, intolerability to multiple CYP metabolized antidepressants, or those receiving antidepressants metabolized via the CYP2C19, CYP2D6, and CYP2B6 pathways.

Acknowledgements

Hector Perez (UCI Research Librarian) for assistance with developing search strategies, Obinna Ekechukwu, Harini Bhat, Jasvir Kaur, for their work on the team with literature screening and data extraction.
The authors wish to thank Dr. Gerard Quinn for reviewing their paper.

Author contributions

MJ- conceptualization of study, edited manuscript CC- conceptualization of study, screened studies, contributed to manuscript preparation and editing FK- screened studies, summarized trial data, drafted and edited manuscript.

Compliance with Ethical Standards

Competing interests
The authors declare no competing interests.

Conflict of Interest
The authors declare no competing interests.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as: • Of importance

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