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Effectiveness of pharmacogenomics on the response and remission of treatment-resistant depression: a meta-analysis of randomised controlled trials

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ABSTRACT

Background Pharmacogenomics (PGx) is a promising tool to realise tailored drug therapy for depression.

Aims To investigate the treatment efficacy of PGx for treatment-resistant depression (TRD) compared with treatment as usual.

Methods A systematic search was conducted in PubMed, Embase, the Cochrane Library, Web of Science and PsycINFO to identify relevant studies published from inception to 15 April 2023. Two-arm randomised controlled trials (RCTs) exploring the efficacy of PGx-guided versus unguided treatment for TRD were included. The risk of bias in the included studies was evaluated using the Cochrane risk of bias assessment tool. The overall quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Results Seven RCTs (n=3003) comparing PGx-guided (n=1492) and unguided (n=1511) groups were identified and analysed. PGx-guided treatment was superior to treatment as usual in response (relative risk (RR)=1.31; 95% confidence interval (95% CI): 1.15 to 1.49; p<0.001) and remission (RR=1.40; 95% CI: 1.09 to 1.80; p=0.009) improvements. Effect sizes for acceptability (RR=0.90; 95% CI: 0.80 to 1.02; p=0.100) and side effect burden (RR=0.58; 95% CI: 0.29 to 1.15; p=0.120) between the two groups were not statistically different. The overall quality of evidence was rated from 'very low' (25%) to 'low' (75%) based on the GRADE criteria.

Conclusions PGx-guided treatment has shown a small overall effect in improving the response and remission rates for patients with TRD. However, these results should be interpreted cautiously because of the few included studies and the low quality of evidence. Further high-quality clinical trials are warranted to confirm the findings.

PROSPERO registration number CRD42022340182.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Treatment-resistant depression (TRD) has often been reported as a significant burden to individuals, families and society. However, there has been a dearth of research on TRD. To date, providing effective antidepressant treatment for the disorder continues to pose complex challenges.

⇒ Pharmacogenomics (PGx) is a promising tool to assist clinicians in appropriate drug selection and provide dosing recommendations to ultimately facilitate reductions in therapeutic response time and adverse drug reaction incidence.

WHAT THIS STUDY ADDS

⇒ Our findings suggest that PGx testing has a small overall effect in improving the response and remission rates for patients with TRD compared with those who received treatment as usual.

⇒ More research on applying PGx tests in 'real world' practice is still needed.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The current evidence is insufficient to support routine PGx testing to guide the treatment of TRD. Thus, the accurate clinical utility of PGx tests for treating TRD awaits further confirmation through independently replicated studies.

INTRODUCTION

Major depressive disorder (MDD), a chronic, incapacitating condition, impacts many individuals worldwide and represents a significant public health concern.[1] The Global Burden of Disease project estimates that depression will become the second leading cause of disability globally by 2030,[2] causing individual suffering, increased healthcare costs, loss of productivity and a rash of suicides.[3] Antidepressant (AD) agents are recommended as the standard of care for treating MDD; however, with limited efficacy in obtaining responses for a certain proportion of individuals, medication therapy outcomes are far from satisfying. According to the data available, about 20%–30% of patients with MDD do not respond sufficiently to adequate treatment of any chosen AD.[4]

Treatment-resistant depression (TRD) was initially delineated by Heimann in 1974.[5] Since then, various definitions of TRD have been proposed. To date, the definition of TRD in the literature is inconsistent. A

recently published systematic review showed that, in total, 155 definitions of TRD were identified in all the related literature.[6] Indeed, in many studies, patients who failed to respond to at least one AD trial of adequate dosage and duration were considered 'treatment resistant'; this condition has been frequently used as an inclusion criterion for clinical trials.[7] TRD is associated with higher recurrence risk, chronicity, comorbidity and suicidal ideation.[8–10] Besides the individual suffering, the enormous economic burden caused by TRD management cannot be neglected. Based on recent literature data, the annual cost of TRD treatment is $43.8 billion in the USA alone, accounting for 47.2% of the entire cost of MDD treatment.[11]

Empirically supported treatment options for TRD are sparse, and the optimal treatment approach for TRD is still debatable. The management of TRD often involves considering and implementing alternative pharmacological agents, various forms of psychotherapy and neuromodulation techniques (such as electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS)).[12] However, ECT—a well-established treatment modality in TRD—and other non-invasive brain stimulation techniques, such as TMS, transcranial direct current stimulation and transcranial alternating current stimulation, as well as psychotherapies are not discussed in the present study. Pharmacotherapy remains a primary mainstream approach due to its well-documented efficacy and user-friendliness in treating depression. Nonetheless, the traditional 'trial-and-error' approach has still been widely used to find the most appropriate treatment for patients with depression. This long protocol process is more likely to lead to initial treatment failure and increase the possibility of TRD occurrence. Personalised medicine takes advantage of individual biotype information to select the optimal treatment and aims to improve therapeutic efficacy and safety; it has garnered much attention in recent decades.[13] At the forefront of precision medicine, pharmacogenomic (PGx) testing is an approach with enormous promise in tailoring pharmacological treatment for patients with depression.[14–16]

PGx has evolved from the convergence of pharmacogenetics with the striking advances in human genomics,[17] studying the contribution of inherited genes and their variation to an individual's medication response phenotype. It has progressed along with the rapid growth in molecular pharmacology and the maturation of genomics during recent decades.[18 19] Until now, pharmacogenetics and PGx usually share similar meanings in many related studies, and they are used interchangeably to indicate the inheritance of variation in drug responses. The content of PGx research often includes pharmacokinetics, assessing genes that impact metabolic enzymes (eg, the cytochrome P450 family), and realising the prediction of drug exposure and proper dosing; and pharmacodynamics, referring to genes that affect neuronal functions, and realising the prediction of drug response and adverse reactions.[18 20 21] Of note, PGx markers based on *CYP2D6/CYP2C19* genotyping are already usable to guide AD selection and dosing according to guidelines provided by several expert consortia like the Clinical Pharmacogenetics Implementation Consortium and others. In addition, these recommendations can standardise and promote the utility of PGx in clinical practice.[22 23]

There is accumulating evidence supporting the effectiveness of PGx in guiding AD therapies for MDD[15 24 25] despite the heterogeneity in the existing studies and clinical applications.[26] Nonetheless, more studies on using PGx in guiding TRD treatment are needed. This meta-analysis was conducted primarily to provide evidence for the efficacy of the PGx-guided approach in treating TRD compared with unguided medication therapy. We also wanted to examine the acceptability of PGx testing among patients with TRD and investigate whether it effectively reduces the side effect burden.

METHODS

Search strategy

This review has been registered in PROSPERO (registration number: CRD42022340182), and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations[27] were used. Two reviewers (YC and HML) conducted a comprehensive search of five electronic databases, including PubMed, Embase, the Cochrane Library, Web of Science and PsycINFO, for studies published from inception to 15 April 2023. Keywords about TRD (eg, depression, treatment-resistant depressive disorder, refractory depression, etc), PGx testing (eg, genetic testing, PGx screening, PGx analysis, etc) and randomised controlled trial (RCT; eg, clinical trial, randomised clinical trial, trial, etc) were used to search the relevant studies. The detailed search strategies are shown in online supplemental table 1. Furthermore, the bibliographies of identified and relevant studies and systematic reviews were screened to ensure all publications were included.

Study selection

The inclusion criteria based on PICOS were used. Participants (P): (1) adult patients (aged over 18) with a primary diagnosis of depression or MDD based on standardised diagnostic criteria (eg, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[28]); (2) patients were required to have experienced at least one prior medication treatment failure due to the lack of clinical efficacy or intolerable adverse events reported by patients or clinicians. Intervention (I): treatment guided by PGx testing. Comparison (C): enrolled participants received treatment as usual (TAU). Outcomes (O): the primary outcome of this current analysis was measured by response and remission rate based on the Hamilton Depression Rating Scale-17 (HDRS-17) (response was defined as a 50% reduction in the HDRS-17 score, and remission was defined as an HDRS-17 score ≤7)[29] or the Clinical Global Impressions Scale (CGI) (remission was defined

as a CGI score of 1 or 2).[30] The secondary outcomes included: (1) the acceptability of PGx, measured by the proportion of patients who dropped out of the study for any reason; (2) the side effect burden of these trials by comparing the number of patients experiencing adverse events or who were classified as having a high level of side effect burden based on standard rating scales (eg, the Frequency, Intensity and Burden of Side Effects Rating Scale[31]). Study design (S): two-arm RCTs comparing treatment efficacy between participants in PGx-guided and TAU groups for TRD. Additionally, comorbidity with other mental disorders (eg, anxiety disorder) was not considered an exclusion criterion. Exclusion criteria were as follows: (1) studies with duplicated data (in this case, only the one with the largest sample or the one with a more complete set would be included); (2) post hoc analyses; (3) research data that were unavailable one month after contacting the authors; (4) studies performed on children and adolescents; and (5) experimental studies, review articles, ecological studies and conference papers.

After removing duplicated studies, two interviewers (YC and HML) conducted two rounds of independent reviews on all identified literature. The title and abstract of each potential study were screened in the first stage, and studies were excluded if both reviewers judged that the inclusion criteria were not met. In the second stage, the full text of the remaining studies was thoroughly examined to ensure their eligibility based on the inclusion and exclusion criteria stated above. Any discrepancies were resolved by discussion between reviewers and the senior author (SY).

Data extraction

Two independent review authors (RY and KY) extracted data from the included studies using the predetermined standard data extraction spreadsheet. The extracted data of each study included the following: first author, publication year, study design, sample size (intervention and control groups), mean age, gender distribution, ethnicity, the mean of previous failed medication trials, targeted genes and main results. When necessary, we emailed the corresponding author for target data and waited a maximum of 30 days for the reply.

Statistical analysis

We performed meta-analyses by synthesising studies that compared the PGx tests to TAU for TRD using the DerSimonian and Laird random effects model.[32] The pooled relative risk (RR) in dichotomous measure with 95% confidence interval (95% CI) was used to assess the effect size of all outcomes. Significance was set at 0.05. The between-study heterogeneity was determined using I^2 statistics and the p value of Q-statistic.[33] Furthermore, a leave-one-out method was used for the sensitivity analysis of the results with high heterogeneity to assess the possible influence of each RCT on the pooled RRs. Publication bias was assessed using a funnel plot and Egger's test.[34] All the current study analyses were performed using RevMan V.5.4 software (Cochrane Information Management System).

Assessment of study quality

Regarding the quality assessment of the included RCTs, we assessed the risk of bias based on Cochrane Collaboration's risk of bias method.[35] The six domains assessed by this method were as follows: random sequence generation (description of the randomisation method), allocation concealment (selection bias), blinding or detection bias, attrition bias, reporting bias (selective reporting of data) and other potential sources of bias. Each domain would be rated as 'high risk', 'unclear risk' or 'low risk'. In addition, the Jadad Scale (range=0–5)[36] was also used to assess the quality of each included RCT. The high and low-quality criteria of the included studies were defined as Jadad scores ≥3 and <3, respectively. Furthermore, to examine the overall evidence of all the outcome measures for this meta-analysis, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system was applied.[37 38] Any disagreement on the quality assessment was resolved through a discussion between RY and KY.

RESULTS

Search results

The initial search of the database yielded a total of 1749 studies. After removing the duplicated studies, 1146 potentially relevant studies were retrieved for screening. After the first round of screening, 49 studies were considered eligible for full-text review. A comprehensive examination of the full-text studies yielded seven RCTs[39–45] published from 2013 to 2021. Forty-two studies were excluded for the following reasons: included patients who had no previous treatment failure (n=9), no related outcome measure (n=27), duplicated studies (n=3) and post hoc analyses (n=3). Finally, seven studies (n=3003) were included in the meta-analysis. A flow diagram of study search and selection is shown in figure 1.

Study characteristics

The characteristics of the included RCTs in this review are summarised in table 1. All the RCTs were parallel-controlled, two-arm studies, and six[39–41 43–45] were registered at the ClinicalTrials.gov website. The studies used different combinatorial PGx tests, and the specific genes included in the tests differed between studies. Despite using various PGx algorithms in these RCTs, it is noteworthy that all the studies in our analysis focused on *CYP2D6* and *CYP2C19*, which are among the most extensively investigated *CYP450* enzyme genes.[46] The mean age of participants ranged from 44.2 to 52.5 years in the PGx group and from 43.9 to 50.7 years in the TAU group. Female participants constituted the majority of both groups, and patients included in our data analysis all reported at least one medication treatment failure.

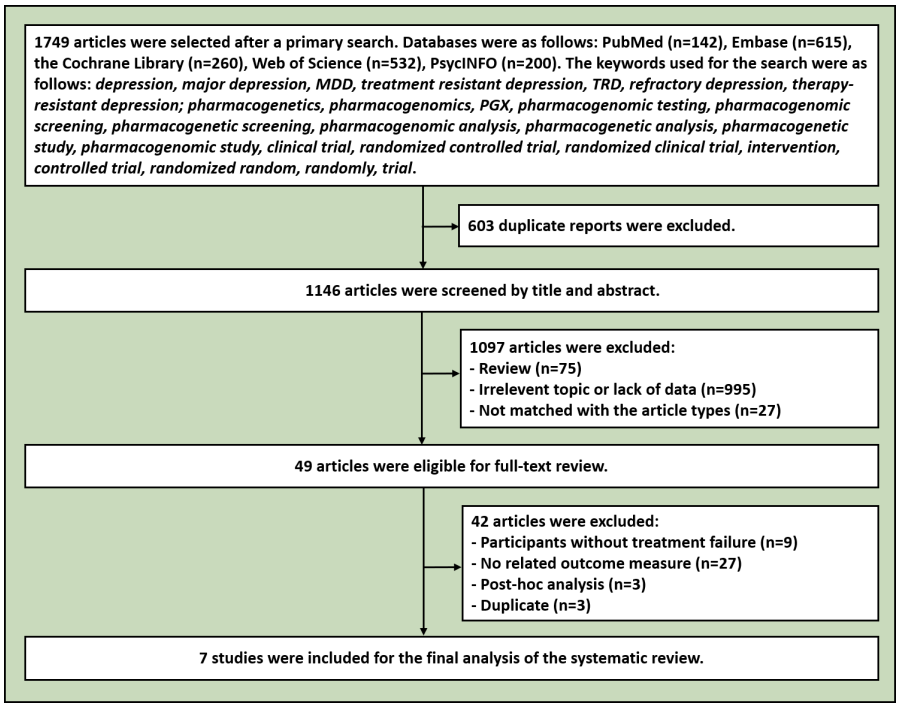

Figure 1 Flowchart of study identification and selection. MDD, major depressive disorder; PGx, pharmacogenomics; TRD, treatment-resistant depression.

Most enrolled patients assigned to both groups in each trial were Caucasians.

Quality assessment

Among the seven RCTs included, four (57%) reported randomisation with specific descriptions; the remaining were considered unclear. Participants were all blinded to the study group. In contrast, the treating physicians in all studies were unblinded to the assignment due to the necessity of using the PGx test reports to guide patient prescriptions (online supplemental table 2). Descriptions of participant withdrawal were provided in four studies (57%), with adverse events, loss to follow-up, protocol violations, out-of-visit window and withdrawal of consent being the reasons cited. Other included studies did not provide any information on reasons for discontinuation. The range of Jadad scores for the included studies was 2–4, with a mean score of 3.3 (table 1). Of the total studies, one (14%) was categorised as low quality, while the remaining studies were deemed to be of high quality (86%). The risks assessed by Cochrane Collaboration's risk of bias method are presented in online supplemental figures 1 and 2. The other detailed risk assessment information for each trial is shown in online supplemental table 2. Based on the GRADE approach, the overall quality of evidence presented for the primary and secondary outcomes varied from 'very low' (25%) to 'low' (75%) (online supplemental table 3).

Meta-analysis results for primary outcome

The response outcome was reported in six trials, as the study by McCarthy *et al*[45] only reported remission rates. The pooled RR for response rate was higher for the PGx-guided treatment than TAU (RR=1.21; 95% CI: 0.99 to 1.47; p=0.060; figure 2A) with no statistical difference. Heterogeneity was moderate across the studies (I^2=59%, p=0.030). The study by Perlis *et al*[44] was identified as a potentially influential case, so we further performed analysis by removing this case, yielding a substantial change in effect size (RR=1.31; 95% CI: 1.15 to 1.49; p<0.001) and heterogeneity (I^2=0%, p=0.660) (see figure 3A).

Remission results were available in all the included studies. The pooled RR was 1.28, comparing the PGx-guided group with the TAU group (95% CI: 0.95 to 1.72; p=0.100; figure 2B), though the difference was not statistically significant. Heterogeneity was also moderate among the studies (I^2=54%, p=0.040). Similar to the processing of response results, analysis was performed by excluding the influential study, showing a significantly higher RR equal to 1.40 (95% CI: 1.09 to 1.80; p=0.009) with low heterogeneity (I^2=24%, p=0.260, see figure 3B).

Meta-analysis results for secondary outcome

The analysis of acceptability measures showed that there was no significant difference in dropouts between the PGx-guided group and TAU group (RR=0.90; 95% CI: 0.80 to 1.02; p=0.100), with a 23.0% dropout rate (343/1492) in the guided arm compared with 25.6% (387/1511) in the TAU arm (see figure 4A). The heterogeneity for this analysis was low (I^2=0%, p=0.830). Data on the burden of side effects were only available in three studies, and the difference in the proportion of patients reporting adverse event burden between the two groups was not significant (figure 4B). The RR was 0.58 (95% CI:

Table 1 Characteristics of included trials

Author and publication year	Study design	Sample size	Age: mean (SD) (guided vs unguided)	Female (%) (guided vs unguided)	Proportion White (%) (guided vs unguided)	Previous failed psychiatric medication trials: mean (SD)	Targeted genes	Main results (guided vs unguided)	Jadad score
Winner *et al*[39] (2013)	▶ A 10-week, prospective, double-blind RCT ▶ Trial registration: NCT01261364	Patients diagnosed with MDD or DDNOS N=51 Guided (n=26) vs unguided (n=25)	50.6 (14.6) vs 47.8 (13.9)	69 vs 92	96 vs 100	4.3 vs 4.5	▶ PGx tools: GeneSight ▶ Targeted genes: *CYP2D6, CYP2C19, CYP1A2, SLC6A4, HTR2A*	▶ Response rate (at week 10) 36.0% vs 20.8%, OR=2.14 ▶ Remission rate (at week 10) 20.0% vs 8.3%, OR=2.75	3
Pérez *et al*[40] (2017)	▶ A 12-week, double-blind, parallel, multicentre RCT ▶ Trial registration: NCT02529462	Patients diagnosed with MDD N=316 Guided (n=155) vs unguided (n=161)	51.74 (12.05) vs 50.74 (13.12)	63.9 vs 63.4	93.5 vs 91.3	2.55 (2.35) vs 2.57 (2.10)	▶ PGx tools: Neuropharmagen ▶ Targeted genes: *CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, ABCB1, AKT1, BDNF, CACNG2, CES1, COMT, CRHR1, DDIT4, DRD3, EPHX1, FCHSD1, GRIK2, GRIK4, HLA-A, HTR1A, HTR2A, HTR2C, LPHN3, NEFM, OPRM1, RGS4, RPTOR, SLC6A4, UGT2B1*	▶ Response rate for the whole sample (at week 12) 45.4% vs 40.3%, p=0.3884 ▶ Remission rate (at week 12) 34.0% vs 33.1%, p=0.8665	4
Bradley *et al*[41] (2018)	▶ A 12-week, prospective, subject-blinded and rater-blinded RCT ▶ Trial registration: NCT02878928	Patients diagnosed with depression or anxiety N=685 Guided (n=352) vs unguided (n=333)	47.8 (14.5) vs 47.3 (15.2)	73 vs 72	63 vs 63	≥1 vs ≥1	▶ PGx tools: NeuroIDgenetix Targeted genes:*CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, SLC6A4, SLC6A4, COMT, HTR2A, HTR2A, MTHFR, MTHFR*	▶ Response rate (at week 12) 64.3% vs 45.5%, p=0.01 ▶ Remission rate (at week 12) for patients with severe depression 35.0% vs 13.2%, p=0.02	3
Han *et al*[42] (2018)	▶ An 8-week, single-blind RCT	Patients diagnosed with MDD N=100 Guided (n=52) vs unguided (n=48)	44.2 (16.1) vs 43.9 (13.8)	76.9 vs 72.9	96 vs 100	2.5 (2.2) vs 2.1 (1.5)	▶ PGx tools: Neuropharmagen ▶ Targeted genes: not stated	▶ Response rate (at week 8) 64.7% vs 39.6%, p=0.014 ▶ Remission rate (at week 8) 39.2% vs 25.0%, p=0.071	2
Greden *et al*[43] (2019)	▶ A large, patient-blinded and rater-blinded randomised controlled study ▶ Trial registration: NCT02109939	Patients diagnosed with MDD N=1398 Guided (n=681) vs unguided (n=717)	46.9 (14.5) vs 48.0 (14.5)	71.8 vs 69.5	79.0 vs 82.1	3.48 (3.09) vs 3.53 (3.01)	▶ PGx tools: GeneSight ▶ Targeted genes:CYP1A2, CYP2C9, CYP2C19, CYP3A4, ▶ CYP2B6, CYP2D6, HTR2A, SLC6A4	▶ Response rate (at week 8) 26.0% vs 19.9%, p=0.013 ▶ Remission rate (at week 8) 15.3% vs 10.1%, p=0.007	4
Perlis *et al*[44] (2020)	▶ An 8-week, multicentre, participant and rater-blinded RCT ▶ Trial registration: NCT02634177	Patients diagnosed with MDD N=304 Guided (n=151) vs unguided (n=153)	47.8 (12.38) vs 47.6 (12.06)	70.9 vs 72.5	73.5 vs 71.9	1 (70.2% vs 66.0%) 2 or 3 (29.1% vs 33.3%) >3 (0% vs 0.7%)	▶ PGx tools: Genecept Assay (version 2.0) ▶ Targeted genes: not stated	▶ Response rate (at week 8) 39.7% vs 48.0%, p=0.17 ▶ Remission rate (at week 8) 24.0% vs 30.7%, p=0.23	4
McCarthy *et al*[45] (2021)	▶ An 8-week, prospective, multisite, single-blind RCT ▶ Trial registration: NCT04469322	Veterans with MDD N=149 Guided (n=75) vs unguided (n=74)	52.5 (1.5) vs 50.3 (1.6)	21 vs 26	73 vs 78	≥1 vs ≥1	▶ PGx tools: CLIA-certified commercial PGx testing facility (Pathway Genomics, San Diego, California, USA) ▶ Targeted genes: *CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, DRD2, HLA, 5HTTLPR, HTR2A, HTR2C, POLG, SLC6A4, UGT1A4*	▶ Remission rate (at week 8) 29% vs 21%, OR=1.54	3

CLIA, Clinical Laboratory Improvement Amendments; DDNOS, depressive disorder not otherwise specified; MDD, major depressive disorder; OR, odds ratio; PGx, pharmacogenomics; RCT, randomised controlled trial; SD, standard deviation.

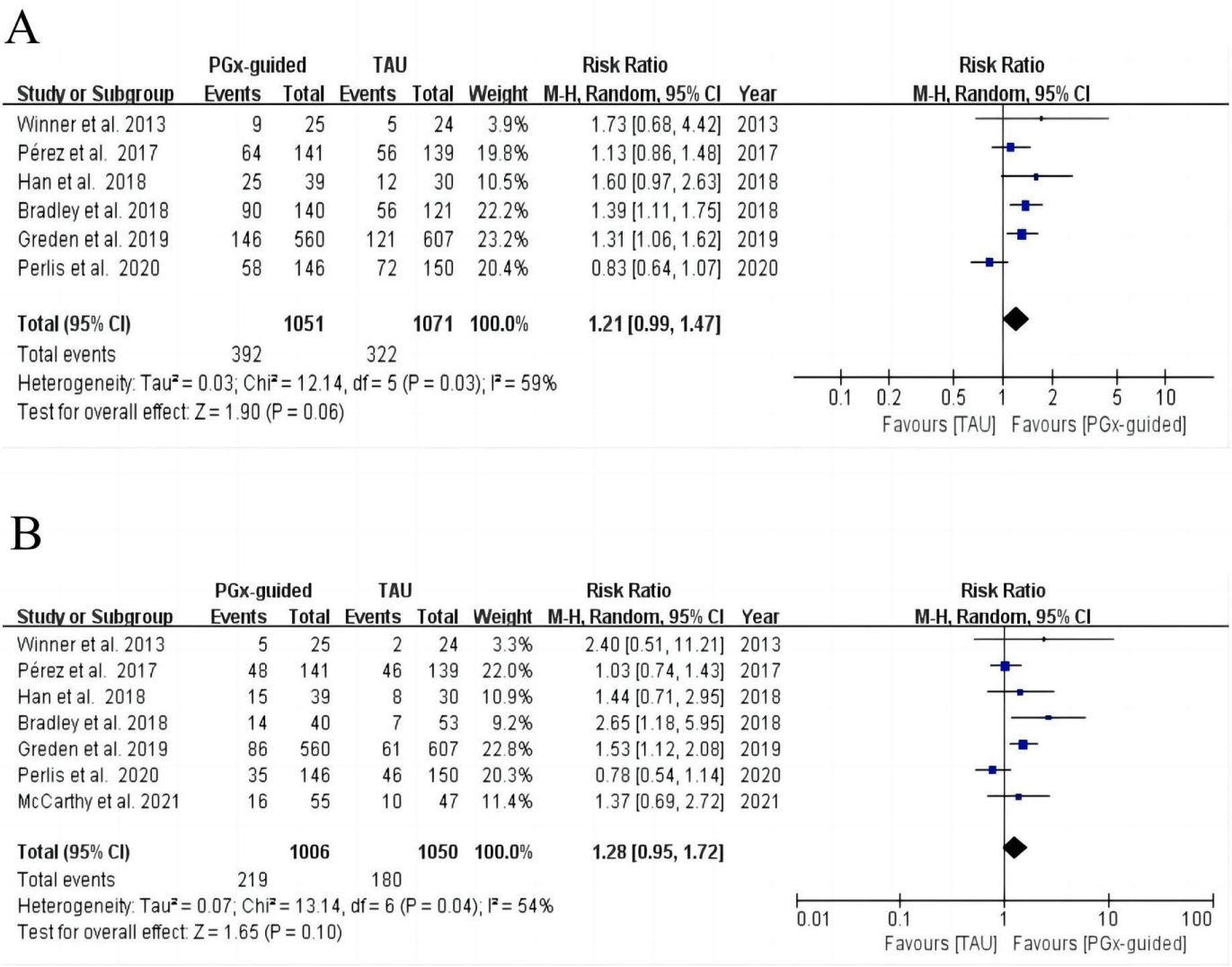

Figure 2 Meta-analysis results of primary outcomes: (A) comparison of the proportion of patients achieving response with guided versus unguided treatment; (B) comparison of the proportion of patients achieving remission with guided versus unguided treatment. CI, confidence interval; PGx, pharmacogenomics; TAU, treatment as usual.

0.29 to 1.15; p=0.120) with high heterogeneity (I^2=84%, p=0.002).

Sensitivity analysis

The results of the sensitivity analysis that used the leave-one-out method suggested that the pooled RR and heterogeneity were not influenced by any single study except the one by Perlis *et al*.[44] Excluding the influential study led to a substantial change in the effect size for response (see figure 3A) and remission (see figure 3B), with a substantial decrease in the I^2 statistic. We also performed a sensitivity analysis for the side effect burden by excluding the study by Han *et al*,[42] as itf was the only study demonstrating a significant difference in the side effect burden between the two groups. However, this did not yield a robust change in effect size or reduction in heterogeneity (see online supplemental figure 3).

Publication bias

Due to the restricted number of RCTs available for the current analysis, it was not feasible to investigate the presence of publication bias.[47]

DISCUSSION

Main findings

This meta-analysis aimed to assess whether adopting PGx testing for TRD improves treatment outcomes compared with usual care. For all we know, this current study is the first to synthesise only RCTs on implementing PGx-guided treatment for patients with TRD. Notably, the inclusion criteria of patients with TRD in each RCT were inconsistent mainly due to the disunity of definitions within the relevant literature.[6] In the present research, any study reporting outcomes of interest for patients with MDD with ineffective or unsatisfactory AD treatment was eligible for analysis. For the primary outcome measures,

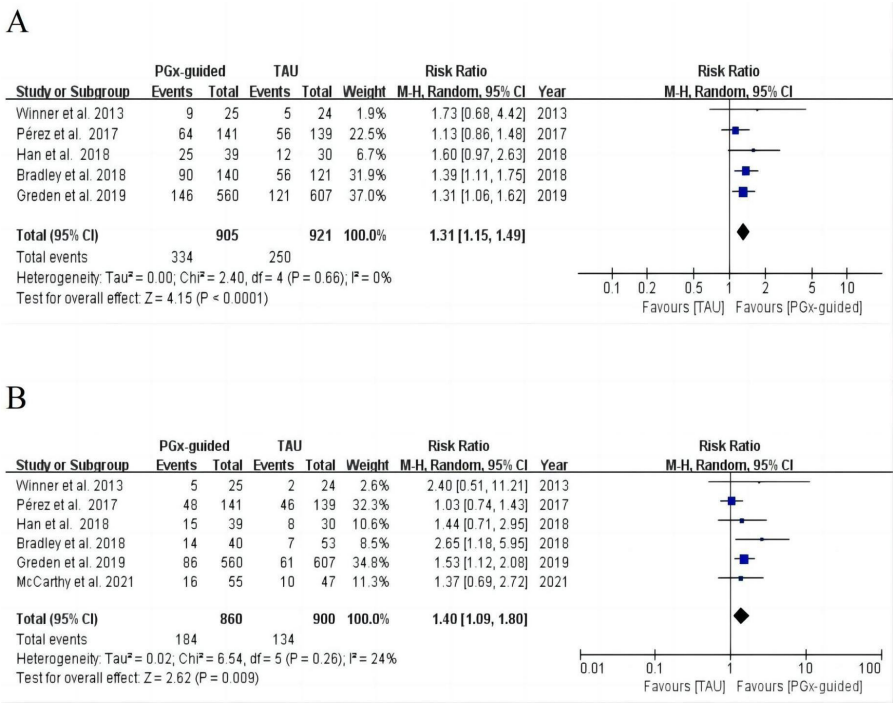

Figure 3 Meta-analysis results of primary outcomes after removing the influential trial: (A) comparison of the proportion of patients achieving response with guided versus unguided treatment; (B) comparison of the proportion of patients achieving remission with guided versus unguided treatment. CI, confidence interval; PGx, pharmacogenomics; TAU, treatment as usual.

we found that the pooled results of all the included studies supported the superior efficacy of PGx testing in improving response and remission rates for patients with TRD compared with TAU. This finding aligns with a prior published meta-analysis[48] exploring the efficacy of PGx in the treatment of patients with MDD who experienced at least one failure in prior drug therapy; however, this previous study only included two RCTs and two open-labelled cohort studies. Of note, we obtained a larger effect size with very low heterogeneity by removing the influential trial by Perlis *et al*,[44] the only case showing that the participants in the guided arm who achieved response and remission were fewer than those in the unguided arm. The potential causes of this outlier might be the enrolment bias and blinding strategy. Nonetheless, there was no valid reason to exclude this trial from our analysis. Regarding the acceptability outcome, more participants in the PGx group dropped out of the trial compared with the TAU group, though there was no statistical difference. As for the side effect burden, although the percentage of participants experiencing adverse events was lower in the guided group (17.2%) than in the unguided group (20.2%), the comparison showed no significant difference.

Although the positive finding regarding response and remission improvement is noteworthy, the quality of the included studies and the outcome evaluation measures were not standardised. Therefore, the results of the present meta-analysis should be interpreted cautiously. Preventing or reducing the side effects associated with ADs is equally, if not more, important than improving the treatment outcomes for the utility of PGx testing. However, the present analysis did not support the expectation that adverse reactions would be reduced, which may be partially due to the different methods used to evaluate them. Indeed, the studies lacked a standard tool for assessing side effects in the PGx studies, thus hindering the ability to replicate findings.[49]

Limitations

There were several limitations in this meta-analysis. First, there were only a small number of RCTs investigating the efficacy of PGx tests for treating TRD, which may affect the reliability of the conclusions drawn from our analysis. Since the number of studies included was below the suggested threshold of the publication bias analysis, it is unclear to what degree this unavailability bias impacts the conclusions. Second, the overall quality of evidence presented for the outcomes implies a low level of confidence in our findings, potentially affecting the reliability of our interpretation and conclusions regarding the measured results. This uncertainty could stem from study design, sample size, methodological issues or other factors not considered, highlighting the need for more high-quality evidence to support the conclusions. Third, all the RCTs included were partially or fully funded by the manufacturers of the PGx tests, which might somewhat limit the persuasion of the results. Another limitation was the lack of long-term follow-up in the included trials, which may influence the assessment of the long-term efficacy of treatment guided by PGx tests. To our knowledge, no published study has reported blinded results beyond

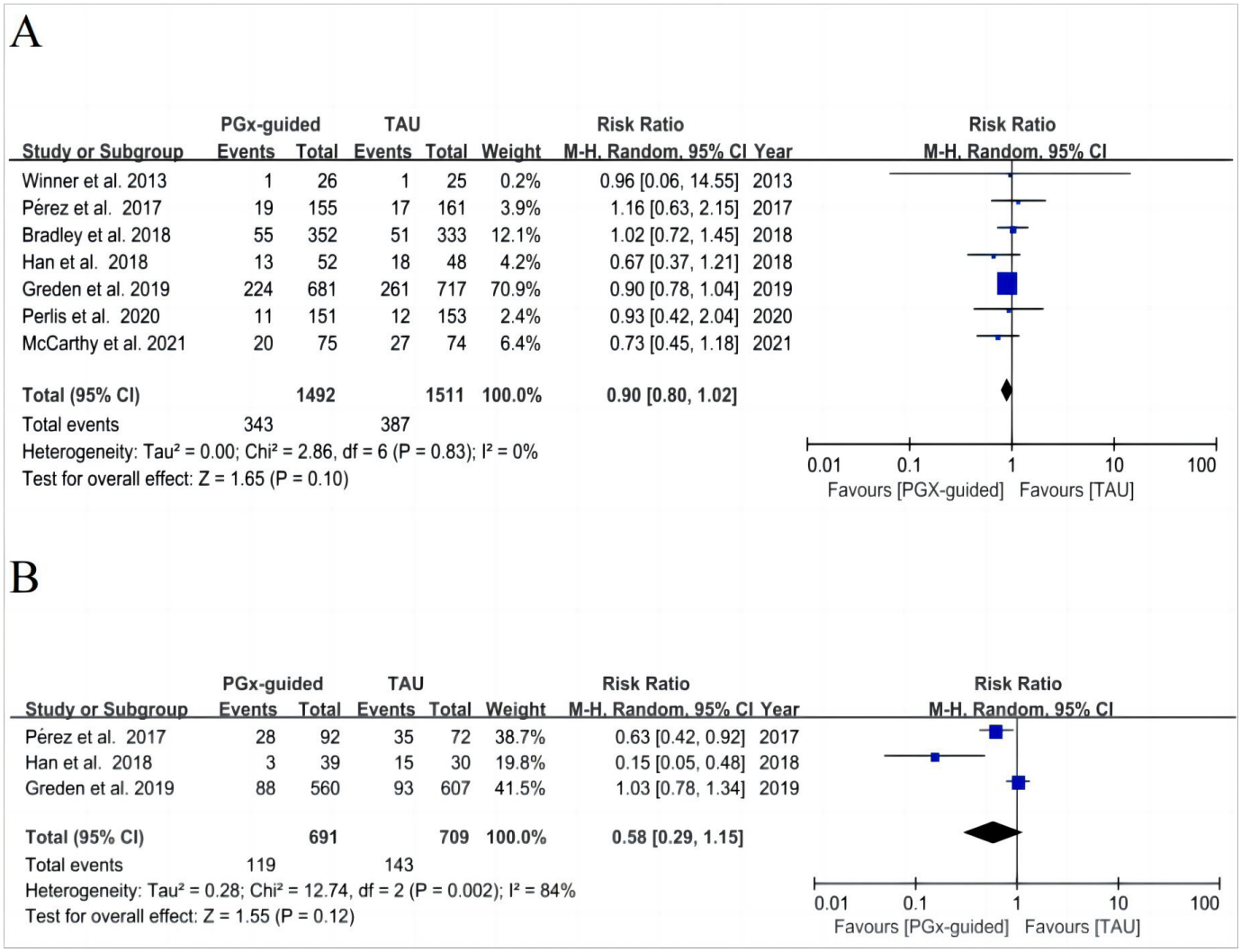

Figure 4 Meta-analysis results of secondary outcomes: (A) comparison of acceptability outcomes (dropout for any reason) with guided versus unguided treatment; (B) comparison of side effect burden with guided versus unguided treatment. CI, confidence interval; PGx, pharmacogenomics; TAU, treatment as usual.

12 weeks, as most studies conducted a blinded protocol for 8 weeks. Given the need to capture the long-term impact of PGx testing, it is essential to conduct more extended follow-up studies to further validate the efficacy of PGx in clinical settings. Finally, the restriction to English language publications could introduce a source of bias or under-representation in our findings.

Implications

Using PGx testing to discern patients' distinct genetic profiles can aid in tailoring therapy, optimising therapeutic effectiveness, minimising adverse reactions and, thus, assisting physicians in making informed medication selections for treating TRD. Increasing evidence has shown that the treatment outcome of the PGx-guided groups is better than that of the TAU groups in patients with MDD.[15 24 25] However, several potential caveats should be weighed before applying PGx for TRD treatment in clinical practice.

First, TRD has a wide variety of underlying factors yet to be elucidated, and its clinical heterogeneity may complicate the interpretation of results when using PGx. In other words, we cannot be sure whether the finding that more patients achieved response or remission in the guided group was due to the utility of the PGx tools. Second, it should be noted that the generalised application of PGx tests in routine practice remains controversial, which can probably be ascribed to the highlighted limitations of the existing studies: the limited sample sizes and ethnicity (the majority of data are from the Caucasian population), poor control of confounders, heterogeneity in study designs and different standards of outcome measures.[50 51] Although evidence from RCTs is commonly recognised as the highest level of substantiation,[52] extending conclusions from RCTs to practical medical care is difficult due to limited external validity.[53] Furthermore, obtaining high-quality RCT evidence is challenging, considering the lengthy time and high cost of large-scale RCTs. In recent years, real-world research has attracted increasing attention. Real-world evidence (RWE) can be obtained from various sources and best

reflects routine clinical practice.[54 55] More significantly, studies have shown that RWE and RCT evidence are complementary and can be regarded as the same level of evidence if the real-world research is well designed and the evidence is used correctly.[53 56] Thus, RWE holds much potential to supplement traditional clinical trials or RCTs to prove further the efficacy of PGx for treating psychiatric disorders. Third, all of the included study participants were over 18, excluding the younger population affected by MDD. Statistics indicate that the lifetime prevalence of MDD among adolescents aged 13–18 in the USA is 11.0%,[57] and approximately 40% of adolescents do not respond to the first trial of an AD.[58 59] Therefore, the implementation of PGx for children and adolescents with MDD warrants further study. Furthermore, many clinicians lack knowledge of genetics or PGx, creating a barrier to the general application of PGx.[60 61] Therefore, to ensure increased and accurate use of PGx tests, clinicians are encouraged to learn the relevant background knowledge of PGx and receive support from pharmacists, genetic counsellors and PGx testing manufacturers.[62] Another issue is the economic cost-benefit; previous studies have suggested that PGx-guided therapeutic management of MDD may lead to cost savings.[63] Heretofore, many studies have primarily focused on assessing the safety and efficacy of PGx testing; it is recommended that future research should include broader economic considerations. Finally, precision medicine still faces a significant challenge in determining which type of patients may benefit the most from PGx testing. Although one previous study suggested that patients with moderate to severe depressive symptoms were more likely to experience symptom improvement under PGx-guided care,[41] no other studies have reached relevant conclusions. Further explorations are required to address precisely where precision medicine can work best.

CONCLUSIONS

This meta-analysis suggests that PGx-guided treatment has a small overall effect in improving response and remission rates for patients with TRD. Though without significant difference, it additionally indicates that the side effect events in the PGx group in most studies are less than those in the control group, indicating the safety of PGx tests. However, considering the included studies' small sample sizes and methodological limitations, physicians must carefully implement the PGx tests when treating patients with TRD and cautiously interpret the testing results. Further research on the real-world application of PGx tests is still needed to narrow the gap between the research findings and the clinical adoption of PGx tests.

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