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Effectiveness of pharmacogenomic tests including *CYP2D6* and *CYP2C19* genomic variants for guiding the treatment of depressive disorders: Systematic review and meta-analysis of randomized controlled trials

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**Abstract**

Major depressive disorders are prevalent conditions with limited treatment response and remission. Pharmacogenomics tests including *CYP2D6* and *CYP2C19* genomic variants provide the most reliable actionable approach to guide choice and dosing of antidepressants in major depression to improve outcome. We carried out a meta-analysis and meta-regression analyses of randomised controlled trials evaluating pharmacogenomic tests with *CYP2D6* and *CYP2C19* polymorphisms in major depression.

A systematic review was conducted according to PRISMA and Cochrane guidelines to search several electronic databases. Logarithmically transformed odds ratios (OR) and confidence intervals (CI) for improvement, response and remission were calculated. A random-effects meta-analysis and meta-regression analyses were subsequently carried out.
Twelve randomised controlled trials were included. Pharmacogenomic tests in the treatment of depression were more effective than treatment as usual for improvement (OR:1.63, CI: 1.19-2.24), response (OR: 1.46; CI: 1.16-1.85) and remission (OR: 1.85; CI: 1.23-2.76) with no evidence of publication bias. Remission was less favourable in recent studies. The results are promising but cautious use of pharmacogenomics in major depression is advisable. PROSPERO registration ID: CRD42021261143.

**Key words:**
Pharmacogenomics, pharmacogenetics, CYP450, CYP2D6, CYP2C19, depressive disorders, major depression, mood disorders.

### 1. Introduction

There is great need to improve treatment in major depression, a common condition with a high life-long prevalence and low response and remission rates. The frequency of depressive disorders, the unsatisfactory response to treatment, the high risk of recurrence and the chronicity reduce quality of life and contribute to premature death in affected individuals (WHO, 2002) (Ferrari et al., 2013) (Cleare et al., 2015).

Research conducted in community samples suggests that remission rates in major depression decline with an increasing number of treatment steps (Rush et al., 2006) (Warden et al., 2007). Personalised pharmacological treatment is a recent approach to improve response and remission in major depression whilst reducing the occurrence of adverse events. Pharmacogenomic evaluation is based on genetic tests that establish the impact of variants of genes affecting the pharmacokinetics and pharmacodynamics of drugs to guide choice and dosing of prescribed pharmacological compounds to treat the disorder. The aim of this approach is to increase the chance of response with the least possible adverse reactions. This is particularly relevant in case of treatment refractoriness in major depression, generally requiring a more aggressive use of pharmacology and inevitably polypharmacy. This common approach increases the risk
of adverse effects and negatively reduce adherence to treatment ultimately worsening clinical outcome (Cleare et al., 2015).

In depressive disorders, gene-drug interactions have been investigated in controlled and open label studies with mixed results. The heterogeneity of the results is related to the variance of study design, clinical and demographic characteristics of the participants, the type of pharmacogenomic tests utilised and the different genes evaluated. The most reliable actionable genetic information for antidepressants, provided by the Clinical Pharmacogenomics Implementation Consortium (CPIC; www.cpicpgx.org) is based on guidelines placing genomic variants of CYP450 family of liver enzymes CYP2D6 and CYP2C19 at the centre of evidence-based recommendations for selective serotonin reuptake inhibitors and tricyclics antidepressants (Hicks et al., 2015) (Hicks et al., 2017). These CYP450 genomic variants provide the most robust evidence for personalised pharmacological treatment in major depression supported by the US Food and drug administration providing labelling information for gene-drug interactions (Smith and Nemeroff, 2020).

Previous work evaluating the effectiveness of pharmacogenomic interventions in comparison with treatment as usual in major depression, has generally been supportive with an effect size for response ranging around 1.14-1.40 and 1.49-1.74 for remission (Bousman et al., 2019) (Rosenblat et al., 2018). Effect size variability depends on the type of tests considered, the number of studies included and whether these were controlled or open label studies.

This systematic review and meta-analysis appraise current evidence from 1) randomised controlled studies that compared a pharmacogenomic guided approach with treatment as usual in major depression and 2) pharmacogenomic tests that included CYP2D6 and CYP2C19 genomic variants to guide the choice of antidepressants. These CYP450 enzymes constitute the highest possible actionable evidence for personalised pharmacological treatment to date. We hypothesised that the selective inclusion of randomised controlled trials which tested polymorphisms with the strongest evidence, combined with a
larger pool of studies, would translate into a larger effect size, supporting the clinical effectiveness of pharmacogenomic interventions in depressive disorders.

2. Materials and Methods

2.1 Querying strategy

A comprehensive literature querying strategy was developed by a medical librarian specialized in systematic reviews (LÖ) and peer reviewed by subject specialist (DA) to include studies from the databases’ inception and up to October 2022 without language restrictions. Six biomedical databases were systematically searched including PubMed, APA PsycInfo, Scopus, Web of Science, EMBASE, and Cochrane Library. To maximize scientific rigour, peer reviewed published studies rather than grey materials were preferred for inclusion (Morley and Grammer, 2021). PubMed and PubMed’s MeSH were used to systematically identify search-term variations. A combination of the search-fields “title”, “abstract” and “MeSH/Thesaurus” identified the best results. Key search terms included ‘Randomized Controlled Trial’ OR ‘Double Blind Controlled Trial’ AND ‘Major depression’ OR ‘Mood Disorders’ OR ‘Affective Disorders’ AND ‘CYP2C19’ OR ‘CYP2D6’ OR ‘Pharmacogenomics’ OR ‘Pharmacogenetics’ (see Supplementary material). All records were uploaded to the systematic review software Covidence (Veritas Health Innovation, 2020, https://www.covidence.org) for automatic de-duplication and blinded screening by two independent reviewers (DA and SJ). Selection discrepancies were resolved in the software by a third reviewer (TA). Identified papers meeting the inclusion criteria were extracted and cross-referenced. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), PRISMA-S extension and Cochrane Handbook for Systematic Reviews of Interventions were adopted for the selection and reporting of the literature (Higgins and Cochrane Collaboration, 2020) (Page et al., 2021) (Rethlefsen et al., 2021). The results of the search and de-duplication are synthetized in a PRISMA
flow-diagram (Page et al., 2021) (Figure 1). PROSPERO registration was granted for this systematic review and meta-analysis (ID: CRD42021261143).

2.2 Eligibility criteria and data extraction

The queries identified randomised controlled trials comparing pharmacogenomic interventions containing genetic testing for cytochromes *CYP2C19* and *CYP2D6* with treatment as usual to guide treatment of major depressive disorders. Studies required that treatment was in the context of a current episode of depression evaluated by using validated rating scales. Studies that presented post-hoc evaluations of data were excluded. In case of multiple publications, the data set with the largest sample size which excluded post-hoc analyses was included. Outcome measures for inclusion were improvement, response and remission of depressive symptoms defined according to clinical criteria based on reduction in rating scale scores. The studies needed to evaluate antidepressant treatment that could be prescribed either in monotherapy or in conjunction with other compounds. There was no specific limitation in terms of level of treatment resistance for inclusion and the possibility of co-morbidities. The main outcome measure was a binary outcome of improvement/response/remission based on a reduction in depression rating scores at endpoint in the intervention group, compared to treatment as usual.

2.3 Data quality appraisal

Two independent assessors screened and reviewed all the articles captured by the search (DA and TA). A third author resolved conflicts by consensus (SJ). Data extraction was carried out by a fourth author (RR) and confirmed by an independent reviewer (RD/SJ). Quality assessment of the selected manuscripts was conducted by using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) by two authors operating independently from each other (DA and SJ). Conflicts were resolved by a third author (RD) (Sterne et al., 2019).
2.4 Data synthesis and analysis

A random effect meta-analysis was conducted with STATA 17.0 (Stata Corp, College Station, Texas) supplemented by ‘Metan’ software v4.02 (David Fisher, MRC Clinical Trials Unit at UCL, London, UK) as previously described (Arnone et al., 2009) (Arnone et al., 2012) (Arnone et al., 2018) (Arora et al., 2022). In brief, we calculated logarithmic transformed odds ratios and 95% confidence intervals for response and remission of pharmacogenetic guided treatment in comparison with treatment as usual. Jack-knife method by leaving one study out was used to evaluate the contribution of each study to the analyses. The Q-test evaluated the presence of heterogeneity. If the Q-test was significant, the proportion of effect size attributable to heterogeneity was calculated with $I^2$ (Higgins et al., 2003). Clinical and demographic variables which were available for consideration in meta-regression analyses included: year of publication, age, sex (% of women), type of test (commercial or non-commercial), randomisation (single or double bind), duration of the study, number of depressive episodes, percentage of Caucasian/White participants, failed medication trials prior to randomisation, duration of the depressive episode, severity of depression, presence of adjunctive pharmacological treatments aside antidepressants, presence of comorbidities. The Egger’s test was used to evaluate the occurrence of publication bias with a significance level set at $p<0.05$ (Egger et al., 1997).

3. Results

3.1 Selection and inclusion of studies

Our literature search identified 1,670 studies, 87 of which were eligible, 45 were appraised and 12 were randomised controlled trials suitable for inclusion (Winner et al., 2013) (Singh, 2015) (Pérez et al., 2017) (Bradley et al., 2018) (Greden et al., 2019) (Shan et al., 2019), (Han et al., 2018) (Perlis et al., 2020) (Papastergiou et al., 2021) (McCarthy et al., 2021) (Oslin et al., 2022; Tiwari et al., 2022), five single and
seven double-blind (Figure 1). A total of 2,877 participants were treated with the pharmacogenomic protocol and 2,808 with standard clinical care. The average age in the intervention group was 45 years, largely constituted by Caucasians or White individuals, and 61% women. The duration of the studies ranged from eight to 26 weeks with an average of 12 weeks and a mode of 8 weeks. Eleven studies included participants who were recruited having failed or poorly tolerated previous treatment trials, five studies reported the number of unsuccessful pharmacological treatments with an average of 3 failed trials. In eleven studies antidepressants were co-prescribed with other compounds. The study by McCarthy and colleagues evaluated depression although the primary presentation varied from unipolar major depression to bipolar disorder with a minority of patients presenting with depression in the context of a diagnosis of post-traumatic stress disorder (McCarthy et al., 2021). Most of the studies assessed response and remission utilised a reduction in rating scale scores from baseline to endpoint expressed as a minimum of 50% reduction for response and subclinical scores for remission. Oslin and colleagues used 5 as a PHQ-9 cut off for remission (Oslin et al., 2022). Perez and colleagues and McCarthy and colleagues used clinicians’ impression of improvement as primary outcome with cut offs suggesting significant improvement (Pérez et al., 2017). Papastergiou and colleagues used improvement as only outcome measure without setting a specific cut off score (Papastergiou et al., 2021). Quality assessment suggested that 6 studies were at low risk of bias whether 6 presented some concern. Result of the analyses for improvement, response and remission rates of pharmacogenomic interventions versus treatment as usual are presented below and Figures 2-4.

3.2 Improvement

Five studies measured improvement, expressed as reduction of rating scale scores over time. The effect size of the analysis indicated that the odds of improvement for those treated with a pharmacogenomic approach were 1.63 times higher compared to the conventional approach (CI: 1.19-2.24) without evidence of publication bias (p=0.41). There was no evidence of heterogeneity in this analysis ($I^2=2.7\%$; df: 4; Q: 7)
4.11; p=0.39). Jack-knife sensitivity analysis suggested a larger contribution of Perez and colleagues’ study.

3.3 Response

Nine studies were included in this analysis suggesting that a pharmacogenomic approach had higher odds of 1.46 times to respond to treatment compared to a non-guided approach (CI: 1.16-1.85), without evidence of publication bias (p=0.43). The analysis indicated evidence of a modest level of heterogeneity ($I^2=52.6\%$; Q: 16.89; df: 8; p=0.031) which was not explained by the variables extracted from the studies in meta-regression analyses (all ps>0.05). Jack-knife sensitivity analysis suggested exclusion of a study each time did not change the result.

3.3 Remission

Ten studies were included in this analysis. The effect size suggested that depressed individuals treated according to a pharmacogenomic approach had higher odds of 1.85 times to respond to antidepressants compared to a non-guided approach (CI: 1.23-2.76), without evidence of publication bias (p=0.25). The analysis indicated the presence of a substantial level of heterogeneity ($I^2=75.8\%$; Q:37.11; df: 9; p<0.001). Meta-regression analyses suggested that the effect size was smaller in more recent studies (Coeff.: -0.2; t: -2.87; p=0.021). Jack-knife sensitivity analysis suggested exclusion of a study each time did not change the result.
4. Discussion

This work evaluated the effectiveness of pharmacogenomic interventions which included the CYP450 family *CYP2D6* and *CYP2C19* genomic variants to inform pharmacological decision in the treatment of major depressive disorders.

The strongest evidence for pharmacogenomic guided treatment choices in major depressive disorders is based on *CYP2D6* and *CYP2C19* genomic variants. Current data suggest: 1) P450 cytochromes *CYP2D6* and *CYP2C19* are heavily involved in the metabolism of commonly prescribed antidepressants (Müller et al., 2013) (Solomon et al., 2019); 2) genomic variants of these enzymes can predict clinically relevant metabolic phenotypes with a direct impact on pharmacokinetic parameters and potentially explain up to 50% of adverse drug reactions (Phillips et al., 2001) (Samer et al., 2013) (Hicks et al., 2015) (Hicks et al., 2017); 3) No single-nucleotide polymorphism from genome-wide association studies has sufficient evidence to support its use in pharmacogenomics tests to guide the treatment of major depression (Corponi et al., 2019).

In agreement with the above, current guidelines for the use of genetic tests in major depression, issued by the CPIC, are based on *CYP2C19* and *CYP2D6* polymorphisms (Hicks et al., 2015) (Hicks et al., 2017). This approach is also supported by the International Society of Psychiatric Genetics (ISPG) (ISPG, 2019) and the Food and Drug Administration (FDA) which has issued labelling recommendations for antidepressants drug-gene interactions (Conrado et al., 2013) (Solomon et al., 2019).

In summary, to date there is no strong evidence-based data to support the standard use of pharmacogenomic tests to guide pharmacological treatment in major depression aside *CYP2C19* and *CYP2D6* polymorphisms. In 2018 the FDA warned clinicians and patients about the uncertainty in the effectiveness and predictive value of pharmacogenomic tests in the treatment of major depression (Smith and Nemeroff, 2020) (Shuren and Woodcock, 2018).
To our knowledge the studies included in this meta-analysis considered \textit{CYP2C19} and \textit{CYP2D6} genomic variants in their guided approach. Results from our work suggests that personalised prescribing based on pharmacogenomic testing which include \textit{CYP2C19} and \textit{CYP2D6} polymorphisms is a valuable addition to personalised pharmacological treatment of depressive disorders. Data from this meta-analysis suggests that, in the absence of publication bias, improvement, response and remission in major depression are 1.46-1.85 times more likely to occur if pharmacogenomic testing is used and that the likelihood of success is the highest for remission. Furthermore, meta-regressions suggested that the effect size for remission decreases with more recent studies being published.

As predicted, our results are of a larger magnitude compared to previous similar work and most consistent with a meta-analysis of randomised controlled studies published in 2019 which evaluated 5 randomised controlled trials testing the overall effectiveness of pharmacogenomic testing. This work reported an effect size for remission of 1.71 (CI: 1.17-2.48; p=0.005) (Bousman et al., 2019).

Our findings are less comparable with a recent meta-analysis which included open label studies and post hoc-analyses of the same data, suggested an effect size of 1.49 for response (CI: 1.29-1.73) and 1.78 for remission (CI: 1.50-2.10) (Ielmini et al., 2022) and an earlier meta-analysis which also included open label studies and suggested a pooled risk ratio of 1.36 for response (CI: 1.14-1.62) and 1.74 for remission (CI: 1.09-2.77) (Rosenblat et al., 2018).

The systematic review of the studies included in our current meta-analysis suggests that pharmacogenomic-guided treatment was largely provided to individuals who had failed previous treatments (>2) or experienced previous adverse events leading to discontinuation of treatment. Participants also frequently suffered previous episodes of depression. Hence, the current indication for the use of a pharmacogenomic intervention is based on a prevailing profile which resembles a recurrent form of illness with evidence of treatment resistance. The study by McCarthy and colleagues specifically targeted patients with treatment resistant depression (McCarthy et al., 2021). It is not quite clear from the
reviewed literature what response and remission rates might look like if a guided approach was offered from the outset to individuals presenting for the first time with depressive symptoms.

Limitations of this work include the predominance of women in the studies, the restricted age group of the participants and the excess of Caucasian/white individuals. All the above might skew the relevance of the findings beyond what was tested in the trials and suggests the need for more work to include other parameters.

Other factors include the risk of small studies bias even in the absence of statistically significant publication bias. This is because some of the studies with a relatively small number of participants might produce larger treatment effects (Arnone et al., 2012). The finding that more recent studies contributed less to remission rates in the guided group in the meta-regression analyses is supportive of this possibility. Large controlled studies would seem necessary in the future, although there is genuine difficulty in recruiting large samples to carry out high quality mood disorders research (Wise et al., 2016). Even though only randomised controlled trials were included in this meta-analysis, quality assessment suggested the possibility of contamination from bias and confounders. It is interesting for example that protocols for prescribing in the studies were generally flexible, an advantage in personalised medicine, that can also invertedly introduce confounding elements. Not least the fact that most studies allowed additional prescribing aside from antidepressants. Although this reflects common practice in the treatment of major depression especially in case of treatment resistance, it allows the possibility of drug-drug and drug-gene interactions which could have confounded the results. Future studies could consider blood levels to check pharmacokinetic parameters of the drug of interest. Finally, as discussed above, to our knowledge there is no standard pharmacogenomic protocols to action genetic information aside from \textit{CYP2D6} and \textit{CYP2C19} genomic variants and the strongest information pertains to selective serotonin reuptake inhibitors and tricyclics antidepressants.
5. Conclusions

In conclusion, the work presented here suggests that there is scope for considering pharmacogenomic tests to improve response and remission rates in the treatment of major depression. However, it is highly recommendable based on the available evidence that pharmacogenomic tests include *CYP2D6* and *CYP2C19* genetic variants and that treatment is advised based on current CPIC evidence-based guidelines and ISPG and FDA recommendations. The current profile of eligible individuals is based on studies which have largely included Caucasian or white women who have mostly failed previous treatment trials. This is limiting and more studies are required to better define eligibility criteria which could include a range of demographic, clinical and biological variables with pharmacodynamic and pharmacodynamic potential (e.g., diet, smoking status, lifestyle). Finally, there are differences in the content of pharmacogenomic tests and it would seem important to design trials in the future to compare different tests. In the future it is possible that pharmacogenomic tests will become part of a more sophisticated matrix to include other emerging putative biomarkers for treatment response such as inflammation (Strawbridge et al., 2015), endocrine measures (Herane-Vives et al., 2018) and neuroimaging data (Cheng et al., 2017).

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Author contributions

DA conceived the idea, ran the analyses and wrote the first draft of the manuscript. LÓ was involved in the identification of the studies prior to selection. OO reviewed the statistics and advised on and validated the analyses. TA participated in the process of selection of the studies with DA. SJ resolved conflicts by consensus. RR, SJ and RDG reviewed the studies and extracted relevant information. RDG resolved conflicts at the stage of quality appraisal. BA and GPP provided guidance and advised on pharmacogenomics in major depression; AHY and ES provided senior leadership to complete the manuscript. All the authors contributed to and approved the final version of the manuscript.

Declaration of competing interest

AHY is Editor of Journal of Psychopharmacology and Deputy Editor, BJPsych Open. He has delivered paid lectures and advisory boards for the following companies with drugs used in affective and related disorders: Astrazeneca, Boehringer Ingelheim, Eli Lilly, LivaNova, Lundbeck, Sunovion, Servier, Livanova, Janssen, Allegan, Bionomics, Sumitomo Dainippon Pharma, COMPASS, Sage, Novartis, Neurocentrx Principal Investigator in the Restore-Life VNS registry study funded by LivaNova. He is principal investigator on: ESKETINTRD3004: “An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression.”, “The Effects of Psilocybin on Cognitive Function in Healthy Participants”, “The Safety and Efficacy of Psilocybin in Participants with Treatment-Resistant Depression (P-TRD)”. He is UK Chief Investigator for Novartis MDD study MJ821A12201. Grant funding (past and present) include NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund
(Canada); MSFHR (Canada); NIHR (UK). Janssen (UK) EU Horizon 2020. No shareholdings in pharmaceutical companies. The other authors have no conflicts of interest to declare.

Data and materials availabilities

Data associated with this paper will be available from DA upon reasonable request.

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Shuren, J., Woodcock, J., 2018. FDA’s Center for Drug Evaluation and Research on agency’s warning to consumers about genetic tests that claim to predict patients’ responses to specific medications.


Identification of studies via databases and registers

Records identified from:

Databases n = 3,012

Records removed before screening: 0
Duplicate records removed by Covidence:

n = 1,342
Records removed for other:

n = 1

Records screened:

n = 1,670

Records excluded:

n = 1,583

Reports sought for retrieval:

n = 87

Reports not retrieved:

n = 0

Reports assessed for eligibility:

n = 87

Reports excluded:

n = 42
19 Wrong study design
16 Wrong outcomes

45 full text studies were screened and 12 met criteria for inclusion in the meta-analysis

Reports excluded:

n = 33
- Genome-wide association studies
- Absence of CYP2D6 and CYP2C19 genomic variants
Figure 1: PRISMA diagram
**Figure 2**: Forest plot showing the effect of pharmacogenomic tests vs. treatment as usual on ‘Improvement’
Figure 3: Forest plot showing the effect of pharmacogenomic tests vs. treatment as usual on ‘Response’
**Figure 4**: Forest plot showing the effect of pharmacogenomic tests vs. treatment as usual on ‘Remission’

**Table 1**: Demographic and clinical characteristics of the studies included in the meta-analysis with specific attention to the intervention group.

*Patents experienced depression in the context of major depression, bipolar disorder and post-traumatic stress disorders. LOCF: Last observation carried forward. ITT: Intention to treat analysis*
Highlights

1) P450 cytochromes *CYP2D6* and *CYP2C19* are heavily involved in the metabolism of commonly prescribed antidepressants, genomic variants of these enzymes can predict clinically relevant metabolic phenotypes with a direct impact on pharmacokinetic parameters and potentially explain up to 50% of adverse drug reactions.

2) This systematic review and meta-analysis appraised current evidence from randomised controlled studies that investigated a pharmacogenomic-guided approach which included *CYP2D6* and *CYP2C19* genomic variants to guide the choice of antidepressants.

3) The results support a cautious use of pharmacogenomics-based therapeutic approaches in major depression.