The Role of Broad Pharmacogenomic Testing in Anxiety Management: a Brief Systematic Review

Background

Anxiety is among the most common psychiatric symptoms, yet management of anxiety can pose a significant challenge for psychiatrists, with potential difficulties including lack of efficacy or treatment resistance, difficulty in assessing 'adequate trial' of interventions, side effects of medications, polypharmacy, and presence of ongoing exogenous contributors to anxiety [1]. Pharmacogenomic (PGx) testing presents an opportunity to augment clinical decision-making with data that can assist treatment by avoiding adverse drug interactions, reducing polypharmacy, and improving likelihood of positive response [2]. PGx testing has demonstrated potential utility in the management of major depressive disorder, with recent meta analysis of 11 clinical trials suggesting that PGx guided treatment had potential benefits in terms of both more rapid response and remission [3], however, trials both including patients with symptoms of anxiety and studies assessing the impact of PGx testing on anxiety symptoms are more limited. The goal of this project is to assess systematically review studies which provide data on the impact of PGx testing on anxiety symptoms.

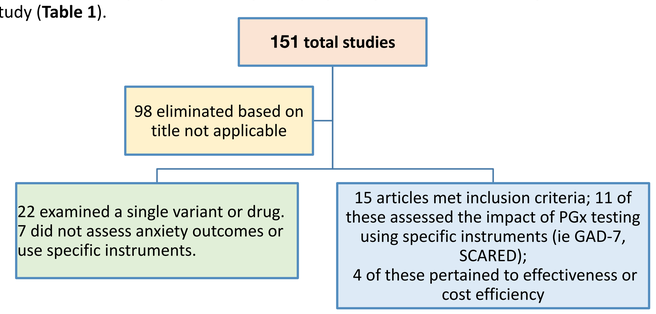
Methods

We performed a systematic literature review of articles in PubMed. Articles were included in the present analysis if they presented results from clinical trials, observational studies, randomized control trials, cohort studies, chart reviews, or prospective studies. Articles were included which assessed the impact of broad PGx testing and either assessed anxiety outcomes using specific instruments or assessed effectiveness or cost efficiency of anxiety management. Of note, studies which evaluated the impact of single polymorphisms related to a single medication were not included.

- The following search term was used in PubMed: (pharmacogenomic* OR pharmacogenetic*) AND (anxiety OR GAD) AND (trial OR ""observational study"" OR RCT OR ""cohort study"" OR ""chart review"" OR prospective study)
- All studies available on 1/16/2024 in PubMed were evaluated

Results

15 studies met criteria: 1 systematic review, 3 prospective, randomized, pragmatic clinical trials, 4 retrospective studies, 1 subanalysis of a 1-year prospective assessment, 2 multicenter analyses, 1 naturalistic, unblinded, prospective analysis, 1 propensity-score matched study, 1 randomized single blind study (**Table 1**).



Discussion

Given significant prevalence and morbidity associated with both primary anxiety disorders and anxiety comorbid with other psychiatric disorders, there is a critical need for novel approaches for treatment and management of anxiety symptoms. The studies included in this analysis provide generally promising results for ways in which PGx testing has the potential to reduce polypharmacy, improve time to response and remission, and reduce overall healthcare costs related to anxiety diagnoses. Nevertheless, there is a severely limited number of clinical studies aimed at investigating the role of PGx testing in anxiety treatment. Further studies are needed regarding PGx-related outcomes among patients with anxiety symptoms or diagnosed with primary anxiety disorders .

Additional References

1. Roy-Byrne P. Treatment-refractory anxiety; definition, risk factors, and treatment challenges. Dialogues Clin Neurosci. 2015;17:191–206.
2. Chanfreau-Coffinier, Catherine et al. "Projected Prevalence of Actionable Pharmacogenetic Variants and Level A Drugs Prescribed Among US Veterans Health Administration Pharmacy Users." JAMA network open vol. 2,6 e195345. 5 Jun. 2019, doi:10.1001/jamanetworkopen.2019.5345
3. Wang, Xinrui, et al. "Effect of pharmacogenomics testing guiding on clinical outcomes in major depressive disorder: a systematic review and meta-analysis of RCT." BMC psychiatry 23.1 (2023): 334.

Acknowledgments

Table 1

Results

Author	Title	Type	Population	Findings
Dagar, A. et. al, 2022	Real-world experience of using combinatorial pharmacogenomic test in children and adolescents with depression and anxiety	Retrospective cohort study	281 patients with depression and anxiety with pre-baseline GeneSight Psychotropic test results	A significant improvement ($p < 0.001$) in Clinical Global Impression (CGI) metrics of severity, efficacy, and global improvement. As a result of CPGx testing, 43.7% of the cohort underwent addition of medication, 32.7% underwent medication replacement, and the rest remained unchanged.
Brown, Lisa et al., 2021	Pharmacogenetic Testing in an Academic Psychiatric Clinic: A Retrospective Chart Review	Retrospective Chart Review	592 patients, 52% with a primary diagnosis of depression, 12% with a primary diagnosis of anxiety who had undergone Pgx testing	There was a reduction in polypharmacy as, prior to PGx testing, 72% of patients reviewed were prescribed 3 or more medications; following PGx testing 44% of patients remained prescribed 3 or more medications ($p < 0.0001$). Incongruence in patient medications was also reduced as, prior to testing, 26% of patients were taking incongruent medications; following PGx testing 19% remained ($p = 0.006$).
Claudio-Campos, Karla et al., 2021	Acceptability, Feasibility, and Utility of Integrating Pharmacogenetic Testing into a Child Psychiatry Clinic	Prospective, randomized, pragmatic clinical trial	49 patients either on medication at baseline and considering a change (38) or open to starting a medication (11)	Poor and intermediate metabolizers for CYP2D6 had higher side effect scores after the 8th week of treatment. Poor and intermediate metabolizers for CYP2C19 had decreasing side effect scores throughout the study as compared to normal metabolizers, rapid metabolizers, and ultrarapid metabolizers. However, when comparing clinical end point between implementation and control arms no differences were reported.
Papastergiou, John et al., 2021	Pharmacogenomics guided versus standard antidepressant treatment in a community pharmacy setting: A randomized controlled trial	Randomized control trial	213 patients diagnosed with MDD or GAD	PHQ-9 total scores were reported over a 6 month period, the overall change was 5.03 and 2.42 between the assay-guided and control groups. These were improvements in baseline depression severity of 36% vs 18%, GAD-7 of 41% vs 23%, and SDS by 44% vs 18%.
Jablonski MR et al., 2020	Economic Outcomes Following Combinatorial Pharmacogenomic Testing for Elderly Psychiatric Patients	Subanalysis of a 1-year prospective assessment	Patients who were utilizing medication regimens congruent or incongruent with PGx testing	Pharmacy claims compared per member per year costs, congruent prescribing resulted in a US$3497 PMPY ($P < .001$) reduction in cost for patients greater than 65 years old and in the prescription of one less neuropsychiatric medication ($P = .070$); congruent prescribing resulted in US$2467 PMPY ($P < .001$) reduction in cost for patients less than 65 years old.
Perlis, Roy H et al., 2020	Randomized, controlled, participant- and rater-blind trial of pharmacogenomic test-guided treatment versus treatment as usual for major depressive disorder	Multicenter randomized double-blind controlled trial	304 outpatients with nonpsychotic MDD who underwent PGx testing followed over 8 weeks	There was no significant difference distinguished in Hamilton Depression Rating Scale (SIGH-D-17) between the assay-guided-treatment and treatment-as-usual arms of the study at the 8 week mark. However, analyses suggested that there was a significant decrease in individuals who had a worsening of depressive symptoms in the assay-guided-treatment arm.
Dunlop, Boadie W et al., 2019	Comparing sensitivity to change using the 6-item versus the 17-item Hamilton depression rating scale in the GUIDED randomized controlled trial	Retrospective study	1541 patients who were the intent-to-treat (ITT) cohort of the Genomics Used to Improve DEpression Decisions (GUIDED) trial	The HAM-D6 distinguished a benefit over treatment as usual in the guided-care arm at 8 weeks ($\Delta = 4.4\%$, $p = 0.023$) while the HAM-D17 did not ($\Delta = 3.2\%$, $p = 0.069$). Both the HAM-D6 ($\Delta = 7.0\%$, $p = 0.004$) and HAM-D17 ($\Delta = 6.3\%$, $p = 0.007$) found a significant increase in response rates for guided-care compared to TAU and greater remission rates (HAM-D6 $\Delta = 4.6\%$, $p = 0.031$; HAM-D17 $\Delta = 5.5\%$, $p = 0.005$). Additionally, HAM-D6 found further increases in benefit over TAU at week 8 for symptom improvement, response, and remission for patients in the guided-care arm who were already utilizing incongruent medications (symptom improvement $\Delta = 7.3\%$, $p = 0.004$, response $\Delta = 10.0\%$, $p = 0.001$, remission $\Delta = 7.9\%$, $p = 0.005$).
Shan, Xiaoxiao et al., 2019	Preliminary Clinical Investigation of Combinatorial Pharmacogenomic Testing for the Optimized Treatment of Depression: A Randomized Single-Blind Study	Randomized single blind study	80 patients with MDD	HAMD-17 testing at baseline, 2, 4, and 8 weeks time points of treatment resulted in no significant difference between assay-guided and treatment-as-usual groups in HAMD-17 scores. Additionally, incidence of adverse reaction was 55.56% in the assay-guided group and 57.89% in treatment-as-usual group.
Bradley, Paul et al., 2018	Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: A randomized clinical trial demonstrating clinical utility	Prospective, randomized, double-blind clinical trial	685 patients with baseline depression or anxiety scores determined by HAM-D17 or HAM-A, respectively	Patients diagnosed with depression response ($p = 0.001$) and remission rates ($p = 0.02$) who underwent NeuroIDgenetix PGx testing were significantly higher than the treatment as usual group at the 12 week assessment using HAM-D17 scoring. Patients diagnosed with anxiety response rates ($p = 0.04$) and HAM-A scores improved at the 8 and 12 week assessments ($p = 0.02$ and 0.02, respectively)
Perlis, Roy H et al., 2018	Pharmacogenetic testing among patients with mood and anxiety disorders is associated with decreased utilization and cost: A propensity-score matched study	Propensity-score matched study	817 patients with a mood or anxiety disorder diagnosis who underwent PGx testing matched to 2745 patients who did not undergo PGx testing	PGx tested patients had 40% fewer all-cause ED visits and 58% fewer inpatient all-cause hospitalizations ($p < 0.0001$ and $p < 0.0001$ respectively). There was no significant difference between the groups in the number of prescribed psychotropic medications or hospitalizations related to mood-based complaints. The tested group was estimated to have $1,948 lower overall 6-month costs as compared to the control group.
Health Quality Ontario: Stacey Brener, Corinne Holubowich, 2017	Pharmacogenomic Testing for Psychotropic Medication Selection: A Systematic Review of the Assurex GeneSight Psychotropic Test	Systematic Review	4 studies examining Assurex GeneSight Psychotropic utility in guiding psychotropic medication prescription	Medication selection guided by the GeneSight Psychotropic test improved responses to depression therapy and represented an increase in prevention of suicide, decrease in depression score, and decrease in lower quality of life score in comparison to patients receiving treatment as usual when measured utilizing the HAMD-17, PHQ-9, or QIDS-C16. No significant difference was found in rates of complete depression remission.
Espadaler, Jordi et al., 2017	Pharmacogenetic testing for the guidance of psychiatric treatment: a multicenter retrospective analysis	Multicenter retrospective analysis	182 patients diagnosed with depression, psychosis, anxiety, or bipolar disorder who received Neuropharmagen PGx testing	Patients who received treatment in congruence with assay results had a 4-fold improvement over control groups who did not receive treatment in congruence with assay results ($p = 0.011$) as measured by CG!-S scores.
Altar, C Anthony et al., 2015	Clinical Utility of Combinatorial Pharmacogenomics-Guided Antidepressant Therapy: Evidence from Three Clinical Studies	Review	258 patients with treatment-resistant depression tested with the GeneSight PGx test during 3 8-10 week 2-arm, prospective clinical trials	Clinical response odds underwent a 2.3-fold increase among all assay-guided subjects as compared to treatment-as-usual subjects ($p = 0.004$). Additionally, the assay guided group had a 53% greater improvement in symptoms ($p = 0.0002$) and a 1.7-fold improvement in response ($p = 0.01$) as compared to the treatment-as-usual group.
Brennan, Francis X et al., 2015	A Naturalistic Study of the Effectiveness of Pharmacogenetic Testing to Guide Treatment in Psychiatric Patients With Mood and Anxiety Disorders	Naturalistic, unblinded, prospective analysis	685 patients who took the Genecept Assay and completed questionnaires at baseline, 1 month, and 3 months	87% of patients experienced clinically measurable improvement and 62% experienced clinically significant improvement as reported by the Clinical Global Impressions-Improvement scale. Patients also reported significant decreases in anxiety ($p < 0.001$), depression ($p < 0.001$), and medication side effects ($p < 0.001$) as well as significant increases in quality of life ($p < 0.001$).
Winner, J et al., 2013	Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression	1 year blinded and retrospective study	96 patients diagnosed with depression or anxiety and on at least 1 common antidepressant/antipsychotic medication	Patients on a medication regimen including a "red bin" drug, as compared to patients with "green bin" or "yellow bin" drugs as determined by the GeneSight Psychotropic test, had 3x more medical absence days, 4x more disability claims, 69% more total healthcare visits, and 67% more general medical visits.