

PERSPECTIVE OPEN



Pharmacogenomic testing for antidepressant treatment selection: lessons learned and roadmap forward

Mark A. Frye¹ and Charles B. Nemeroff²

© The Author(s) 2023

Pharmacogenomic technology is a developing field with enthusiastic interest and broad application potential. Three large, controlled studies have been published exploring the benefit of pharmacogenomically guided antidepressant treatment selection. Though all three studies did not show significant benefit of using this technology, these studies laid the foundation for further research that should address the limitations of this previous research and currently available commercial platforms. Future research needs to include large scale pharmacogenomic trials with GWAS analytics across diverse groups with attention to cost-effectiveness models, particularly for cases of treatment resistance and polypharmacy. The application of results from these large scale pharmacogenomic trials must also include exploring optimal EHR user interface design.

Neuropsychopharmacology (2024) 49:282–284; <https://doi.org/10.1038/s41386-023-01667-4>

INTRODUCTION

Pharmacogenomic decision support tools are an evolving technology that help clinicians make informed decisions, based on clinically actionable genetic variants in pharmacokinetic (PK) and or pharmacodynamic (PD) genes that potentially impact safety, tolerability, and response to medications. The potential value add to the index episode of care is treatment selection based on the patient's biology, not solely relying on FDA indication or off label clinical experience. Most commercially available platforms span multiple PK and PD genes and multiple classes of psychotropic drugs (antidepressant, antipsychotics, stimulants, mood stabilizers). However, antidepressant selection for treatment of major depressive disorder has been the area of most focused research in psychiatry.

MAJOR STUDIES IN THE FIELD

The National Network of Depression Center's GUIDED Trial (Genomics Used to Improve Depression Decisions) enrolled 1167 outpatients in an 8-week, randomized, patient- and rater-blind controlled study of clinician GUIDED antidepressant treatment selection vs treatment as usual (TAU) [1]. There was no difference in the primary outcome measure of mean change in Hamilton Depression Rating Scale (27.2% vs 24.4%, $p = 0.107$) for those participants who completed the study through week 8. Although the utility of secondary outcome measures in the context of a failed primary outcomes measure is of questionable validity [2], secondary outcome measures of response (26% vs 20%, $p = 0.013$) and remission (15% vs 10%, $p = 0.007$) favored GUIDED.

The PRIME CARE Randomized Trial enrolled 1944 patients receiving care at VA medical centers in a 24-week randomized open-label trial of pharmacogenomic guided treatment selection ($n = 966$) vs TAU ($n = 978$) [3]. Educational materials were

provided for test interpretation and consideration for prescribing low risk medications. The co-primary outcome measures were the proportion of prescriptions with a predicted drug-gene interaction written and remission of depression ($\text{PHQ-9} \leq 5$). There was a significant difference with the pharmacogenomic-guided group as they were more likely to receive a medication with a lower potential drug-gene interaction (no drug-gene vs moderate/substantial interaction). Remission rates over 24 weeks were significantly higher for pharmacogenomic care vs TAU, but not significantly higher at week 24. Perlis et al. (2020) conducted a randomized clinical trial of 304 patients with major depression and found no benefit of pharmacogenomic testing [4]. Finally, the first randomized pharmacogenomic testing of depression treatment in adolescents ($n = 176$) found no significant difference in symptom improvement or side effect burden in the pharmacogenomic vs TAU groups [5]. Thus, a comprehensive review concluded that at present time, there is little evidence to support routine use of currently available pharmacogenomic tests in predicting antidepressant response [6].

LIMITATION OF CURRENT COMMERCIAL PLATFORMS AND STUDY DESIGN

These large, controlled studies of pharmacogenomic testing for antidepressant treatment have not shown significant benefit of this decision support technology. It is important to emphasize these investigations were not designed as placebo-controlled investigational studies such as would be anticipated for a submission, for example, to the FDA for a new drug application. Future trial design should review the merits of a "placebo like" arm, but also randomization allocation, not only on treatment resistance and comorbidity, but metabolic capacity, recognizing both P450 metabolizer genotype and additional drugs that

¹Department of Psychiatry & Psychology, Mayo Clinic, Mayo Clinic Alix School of Medicine, Rochester, MN, USA. ²Department of Psychiatry & Behavioral Sciences, University of Texas at Austin Dell Medical School, Austin, TX, USA. ✉email: mfrye@mayo.edu

Received: 23 March 2023 Revised: 23 June 2023 Accepted: 11 July 2023

Published online: 7 August 2023

further induce or inhibit cytochrome metabolism can impact study results [7].

While the primary outcome measure of GUIDED Trial was not met, important exploratory analyses have made a positive impact on future trial design. For example, 912 participants (439 GUIDED, 473 TAU) identified from the original intent to treat cohort at baseline, had a clinically actionable variant or gene-drug interaction categorized as “use with caution” or “used with increased caution and with more frequent monitoring” [8]. Excluding treatment selection that did not pose a gene-drug interaction (i.e., no additional value of genotyping based on treatment selection), GUIDED participants had greater mean change in HDRS than TAU (27% vs 22% $p = 0.029$) as well as response (27% vs 19%, $p = 0.008$) and remission 18% vs 11%, $p = 0.003$). A second exploratory analysis evaluated if the Hamilton-D6, which focused on core symptoms of depression, would be more sensitive to change when exploring a potential biologic variable related to outcome [9]. The HAM-D6 as a continuous measure demonstrated significantly greater percentage decrease at week 8 in the GUIDED group (4.4%, $p = 0.023$); this difference was not present when using the full HDRS (3.2%, $p = 0.069$).

One could argue, given the substantial number of pharmacokinetic (PK) and pharmacodynamic genetic variants, as well as varied treatment selection (GUIDED included 21 antidepressants and 7 antipsychotics, PRIME CARE included 1406 participants who received an antidepressant), these studies were likely underpowered to identify a significant treatment arm difference. One approach to reduce this heterogeneity would be to consider a narrower group of variants or treatment(s), studying biotransformation (PK) and dynamic mechanism of drug action (PD) together. For example, a secondary analysis completed from the STAR*D study focused on depressed participants who prospectively did not achieve remission from the SSRI citalopram and were subsequently enrolled in an SNRI trial of venlafaxine [10]. Remission with venlafaxine, a 2D6 metabolized antidepressant, in prior prospective confirmation of non-remission with citalopram, a 2C19 metabolized antidepressant, was associated with a significant interaction between P450 2D6 ultra-rapid metabolizer phenotype and a greater amount of serotonin *SLC6A4* L/L and noradrenergic *SLC6A2* transporter protein. Single drug studies targeting PK-PD interaction will have greater statistical power and clearly can provide potential clinical value in practice.

From a pharmacokinetic perspective, the bar or level of evidence for safety parameters, such as FDA black box warnings for 2D6 poor metabolizer phenotype and QT prolongation or reduced metabolic conversion of prodrug tamoxifen to chemotherapeutically active endoxifen, is significantly lower than a genetic variant that is a biomarker of treatment response. It is of note that pharmacokinetic variation has contributed to the newly FDA drug for depression treatment, dextromethorphan bupropion combination, both from the standpoint of mechanism of action, with bupropion inhibiting 2D6 increasing dextromethorphan (a NMDA antagonist) levels, as well as clinical guidelines with reduced dosing of the drug with known poor metabolizers at 2D6 (<https://www.axsome.com/auvelity-prescribing-information.pdf>).

From a pharmacodynamic perspective, the black box warning of *HLA-B*1502* variation and carbamazepine-associated Stevens-Johnson syndrome has impacted clinical practice; further work is encouraged to explore potential PD variants related to drug safety. For example, a recent meta-analysis of 7 studies investigating antidepressant-associated treatment emergent mania (TEM) in bipolar disorder identified a significant association between the short or s allele of the serotonin transporter *SLC6A4* and TEM (OR:1.43; 95% CI:1.0–2.06; $p = 0.05$). An important commentary from the author underscored focusing on TEM biomarkers beyond serotonin transporter, highlighting no prior work with norepinephrine or dopamine transporters, and more broadly, but not part of commercial platforms today, genomewide association

studies [11]. Indeed, there are several polymorphisms including the CRH binding protein [12] and the ABCB1 gene [13].

CONCLUSION

Pharmacogenomic testing is a technology that will continue to advance and inherently has potential to transform clinical practice. The roadmap to greater precision in current and future novel therapeutics should be with large scale pharmacogenomic trails employing GWAS analytics and cost-effectiveness models, in particular in cases of treatment resistance and polypharmacy. To address generalizability, future studies need to prioritize diverse groups to look at possible genetic variation by ethnic groups and optimal EHR user interface design. How genomic data is added to large scale databases focused on optimal EHR interface or conventional decision support tools is yet to be determined.

REFERENCES

- Greden JF, Parikh SV, Rothschild AJ, Thase ME, Dunlop BW, DeBattista C, et al. Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: A large, patient- and rater-blinded, randomized, controlled study. *J Psychiatr Res*. 2019;111:59–67. <https://doi.org/10.1016/j.jpsychires.2019.01.003>.
- Andrade C. The Primary Outcome Measure and Its Importance in Clinical Trials. *J Clin Psychiatry*. 2015;76:1320–3.
- Oslin DW, Lynch KG, Shih MC, Ingram EP, Wray LO, Chapman SR, et al. Effect of Pharmacogenomic Testing for Drug-Gene Interactions on Medication Selection and Remission of Symptoms in Major Depressive Disorder: The PRIME Care Randomized Clinical Trial. *JAMA*. 2022;328:151–61. <https://doi.org/10.1001/jama.2022.9805>.
- Perlis RH, Dowd D, Fava M, Lencz T, Krause D. Randomized, Controlled, Participant- and Rater-blind trial of Pharmacogenomic Test-guided Treatment Versus Treatment As Usual for Major Depressive Disorder. *Depression Anxiety*. 2020;37:834–41. <https://doi.org/10.1002/da.23029>.
- Vande Voort JL, Orth SS, Shekunov J, Romanowicz M, Geske JR, Ward JA, et al. A Randomized Controlled Trial of Combinatorial Pharmacogenetics Testing in Adolescent Depression. *J Am Acad Child Adolesc Psychiatry*. 2022;61:46–55. <https://doi.org/10.1016/j.jaac.2021.03.011>.
- Goldberg JF, Nemeroff CB. Pharmacogenomics and antidepressants: efficacy and adverse drug reactions. In: *Psychiatric Genomics* (Tsermpini E, Alda M, Patrinos GP, Editors. Academic Press; 2022, p. 189–202.
- Zeier Z, Carpenter LL, Kalin NH, Rodriguez CI, McDonald WM, Widge AS, et al. Clinical Implementation of Pharmacogenetic Decision Support Tools for Antidepressant Drug Prescribing. *Am J Psychiatry*. 2018;175:873–86. <https://doi.org/10.1176/appi.ajp.2018.17111282>.
- Thase ME, Parikh SV, Rothschild AJ, Dunlop BW, DeBattista C, Conway CR, et al. Impact of Pharmacogenomics on Clinical Outcomes for Patients Taking Medications With Gene-Drug Interactions in a Randomized Controlled Trial. *J Clin Psychiatry*. 2019;80:19m12910. <https://doi.org/10.4088/JCP.19m12910>.
- Dunlop BW, Parikh SV, Rothschild AJ, Thase ME, DeBattista C, Conway CR, et al. Comparing sensitivity to change using the 6-item versus the 17-item Hamilton depression rating scale in the GUIDED randomized controlled trial. *BMC Psychiatry*. 2019;19:420. <https://doi.org/10.1186/s12888-019-2410-2>.
- Ahmed AT, Biernacka JM, Jenkins G, Rush AJ, Shinozaki G, Veldic M, et al. Pharmacokinetic-Pharmacodynamic interaction associated with venlafaxine-XR remission in patients with major depressive disorder with history of citalopram/escitalopram treatment failure. *J Affect Disord*. 2019;246:62–8. <https://doi.org/10.1016/j.jad.2018.12.021>.
- Nuñez NA, Gardea-Resendez M, Melhuish Beaupre L, Coombes BJ, Sanchez Ruiz J, Ozerdem A, et al. Anti-depressant associated treatment emergent mania: evaluating pharmacogenomic targets of potential clinical value. *J Clin Psychopharmacology*. 2024, in press.
- O’Connell CP, Goldstein-Piekarski AN, Nemeroff CB, Schatzberg AF, DeBattista C, Carrillo-Roa T, et al. Antidepressant outcomes predicted by genetic variation in corticotropin-releasing hormone binding protein. *Am J Psychiatry*. 2018;175:251–61.
- Schatzberg AF, DeBattista C, Lazzaroni LC, Etkin A, Murphy GM Jr, Williams LM. ABCB1 genetic effects on antidepressant outcomes: a report from the iSPOT trial. *Am J Psychiatry*. 2015;172:751–9.

AUTHOR CONTRIBUTIONS

Both MAF, MD and CBN MD, Ph.D. Significantly contributed to the following aspects of this work: acquisition, review, and interpretation of literature referenced in this

perspective, drafting the work, revising it critically for important intellectually content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

COMPETING INTERESTS

MAF, M.D. 2023. Grant Support: Assurex Health, Mayo Foundation. Speakers' Bureau: NONE. CME/Travel/Honoraria: Carnot Laboratories, American Physician Institute. Financial Interest/Stock ownership/Royalties: Chymia LLC. CBN M.D., Ph.D. Research/Grants: National Institutes of Health (NIH). Consulting: AbbVie, ANeuroTech (division of Anima BV), Signant Health, Magstim, Inc., Intra-Cellular Therapies, Inc., EMA Wellness, Sage, Silo Pharma, Engrail Therapeutics, Pasithea Therapeutic Corp., GoodCap Pharmaceuticals, Inc., Senseye, Clexio, Ninnion Therapeutics, EmbarkNeuro, SynapseBio, BioXcel Therapeutics, Relmada Therapeutics. Stockholder: Seattle Genetics, Antares, Inc., Corcept Therapeutics Pharmaceuticals Company, EMA Wellness, Naki Health, Relmada Therapeutics. Scientific Advisory Boards: ANeuroTech (division of Anima BV), Brain and Behavior Research Foundation (BBRF), Anxiety and Depression Association of America (ADAA), Skyland Trail, Signant Health, Laureate Institute for Brain Research (LIBR), Inc., Heading Health, Pasithea Therapeutic Corp., Sage. Board of Directors: Gratitude America, ADAA, Lucy Scientific Discovery, Inc. Patents: Method and devices for transdermal delivery of lithium (US 6,375,990B1); Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2). Speakers Bureau: None.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Mark A. Frye.

Reprints and permission information is available at <http://www.nature.com/reprints>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2023