Pharmacogenomic Testing of Complex Psychiatric Cases, including Those with ADHD and Comorbid Conditions, Reveals an Increased Frequency of Abnormal Metabolic Phenotypes, Compared to the General Population.

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Abstract

Patients referred to psychiatrists often present with co-morbidity and a history of previously failed pharmacological treatments. In addition, obtaining positive clinical outcomes with these patients can be challenging as the chances of remission decrease with each failed treatment. Treatment failure can be caused by genetic variability in the genes coding for metabolic enzymes (e.g., cytochrome P450s), which can result in patients experiencing intolerable side effects from overexposure (poor metabolism) or a lack of efficacy from underexposure (ultrarapid metabolism). Using a new pharmacogenomic panel that evaluates 44 genes, including 13 metabolic enzymes, we observed a high frequency of abnormal metabolic phenotypes from a cohort of 137 patients with complex clinical presentations, including those with ADHD and comorbid conditions, compared to expected frequencies in the general population.

For example, CYP2D6 activity, important for clearance of amphetamines and atomoxetine, was reduced in 66% of patients (intermediate and poor metabolizers), about 2-fold higher than that observed in the general population (32%). On average, 6 abnormal phenotypes were observed in each patient (minimum: 3, maximum: 10). These findings suggest a selection bias towards abnormal phenotypes in psychiatric patients with complex clinical presentations, which could contribute to previous pharmacological treatment failures. While drug response is multifactorial, pharmacogenomic testing can provide a baseline on which other factors exert their effect. This could be instrumental in returning to normal functioning, especially in psychiatric patients with co-morbidity and previously failed treatments.

Introduction

For patients with attention deficit hyperactivity disorder (ADHD), pharmacological treatments are part of an integrated and multimodal treatment plan. First-line treatments, consisting of long-acting psychostimulants, are generally safe and effective. However, as with all medications, individual responses vary, and up to 35% of patients do not respond adequately.[1-3] Poor response and adverse drug reactions are often the cause for switching to 2nd-line (atomoxetine, guanfacine XR, short/intermediate acting psychostimulants) and 3rd-line (bupropion, clonidine, imipramine and modafinil) medications. Also, undiagnosed and untreated comorbidity can contribute to inappropriate medication responses. Indeed, 50-90% of children with ADHD have at least one comorbid condition; in adults, the frequency is estimated at 85%.[4-6] In children and adults, psychiatric comorbidities can include anxiety, depression, obsessive compulsive, tic and oppositional defiant disorders.[7] When 1st-line medications generate insufficient or inadequate response, 2nd- and 3rd-line agents may be used alone or in combination with 1st-line medications. Therefore, polypharmacotherapy and off-label use are more common in these patients and those with comorbid conditions, raising the risk of side effects and poor patient outcomes.[8,9]

Pharmacogenomics (PGx) aims to identify individual genetic variation to predict individual patient responses to medications. With most studies focused on pharmacokinetics (cytochrome P450 enzymes, CYPs) and drug exposure, PGx testing can determine a patient's baseline metabolic capacity for each enzyme tested. While in most cases, genomics alone cannot predict with certainty a patient's reaction to medication, PGx results can inform the physician whether any particular enzyme tested has reduced (poor and intermediate metabolizers) or increased activity (rapid, ultrarapid and inducible metabolizers), which would generate higher or lower than expected plasma concentrations, respectively, for a given medication at standard doses, and therefore increased risks of adverse reactions or lack of efficacy **(Figure 1)**.

While preliminary data is available for 1st-line ADHD medications, actionable peer-reviewed PGx recommendations have been published for 2nd- and 3rd-line ADHD medications (including atomoxetine), as well as for medications used to treat common comorbidities, such as serotonin reuptake inhibitor antidepressants, tricyclic antidepressants, and atypical antipsychotics **(Table 1)**.[10-13] Use of these recommendations by physicians has been shown, mainly through studies in patients with major depressive disorder, to help patients return to normal functioning by improving remission rates, improving the effectiveness of therapies and reducing the risks of adverse drug reactions.[14,15] Interestingly, patients with poor and ultrarapid metabolism of their prescribed medications have higher rates of medication discontinuation due to adverse effects and lower efficacy, respectively.[16-18] Based on the observation that patients with PM and UM phenotypes have increased rates of medication discontinuation, we hypothesized that patients referred to psychiatrists that have complex clinical presentations (i.e., comorbidity and previously failed pharmacotherapy) likely have a higher frequency of abnormal phenotypes, compared to expected frequencies in the general population.

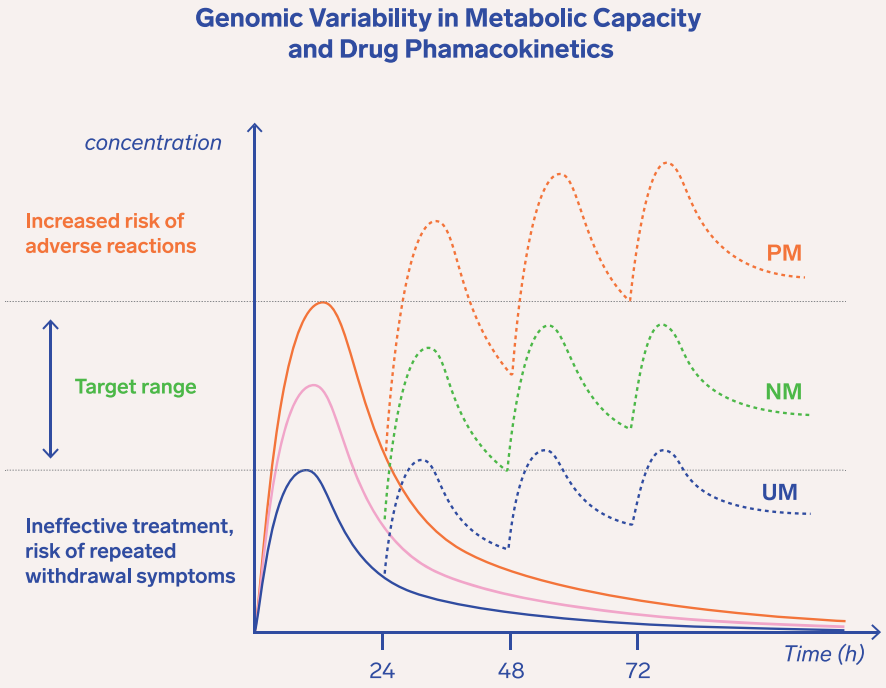

FIGURE 1. Potential effect of metabolic phenotype on exposure to medication over multiple doses.
PM: poor metabolizer; **NM**: normal metabolizer; **UM**: ultrarapid metabolizer.

TABLE 1. Gene-drug interactions for 2nd and 3rd–line ADHD medications, and to treat common comorbidities.

Medications	Gene-Drug Interactions (Published PGx Guideline)	Indications
Atomoxetine	CYP2D6 (CPIC)[19]	2nd-line ADHD medication
Methylphenidate short-acting	CES1	2nd-line ADHD medication
Guanfacine	CYP3A4	2nd-line ADHD medication
Bupropion	CYP2B6, POR	3rd-line ADHD medication
Clonidine	CYP2D6	3rd-line ADHD medication
Imipramine	CYP2C19, CYP2D6 (CPIC)[20]	3rd-line ADHD medication
Modafinil	CYP3A4	3rd-line ADHD medication
Selective Serotonin Reuptake Inhibitors	CYP2D6, CYP2C19, CYP2B6 (CPIC)[21]	Common comorbidities
Antipsychotics (Risperidone, Aripiprazole)	CYP2D6 (DPWG)[22]	Common comorbidities

CPIC: Clinical Pharmacogenetics Implementation Consortium; DPWG: Dutch Pharmacogenetics Working Group.

Methods

Patients were recruited for PGx testing by Canadian specialists (39 psychiatrists and 1 pediatrician) based on their judgement that the test could them (e.g., complex cases with comorbidity and/or a history of failed pharmacotherapy). All patients gave written consent for panel pharmacogenotyping and the use of results for statistical and publication purposes. A saliva sample was collected to apply the commercial pharmacogenotyping service offered by Biron (Brossard, Canada). DNA was extracted using the Maxwell system (Promega) in their laboratory, and the polymorphisms were determined by applying MALDI-TOF-based single nucleotide primer extension genotyping (Agena Biosciences, United States). The applied commercial PGx panel test includes 126 genetic variants, covering genes involved in drug pharmacokinetics and pharmacodynamics (**Table S1**). The interpretation of genotyping results for metabolic enzymes identified patients as normal metabolizers (NM, *1 homozygous) in the absence of a detectable variant.

Results

A total of 137 were recruited for pharmacogenomic testing **(Table 2)**. Although specific diagnostic information was unavailable for all patients, physicians reported recruitment of difficult-to-treat and complex patients, with comorbidities and a history of at least 2 failed pharmacological treatments. Genotyping of the 13 metabolic enzymes revealed that patients had at least 3 abnormal phenotypes, with an average 6 abnormal phenotypes per patient **(Figure 2)**. After a closer look at the frequency of CYP2D6 phenotypes, we found that the frequency of patients with reduced CYP2D6 activity (i.e., IM and PM) was more than twice as high as that expected from the general population **(Figure 3)**.

TABLE 2. Patient characteristics (N=137).

Female	**64** (47%)
Male	**73** (53%)
Age (years)	Average: **38** Median: **39** Minimum: **7** Maximum: **84**

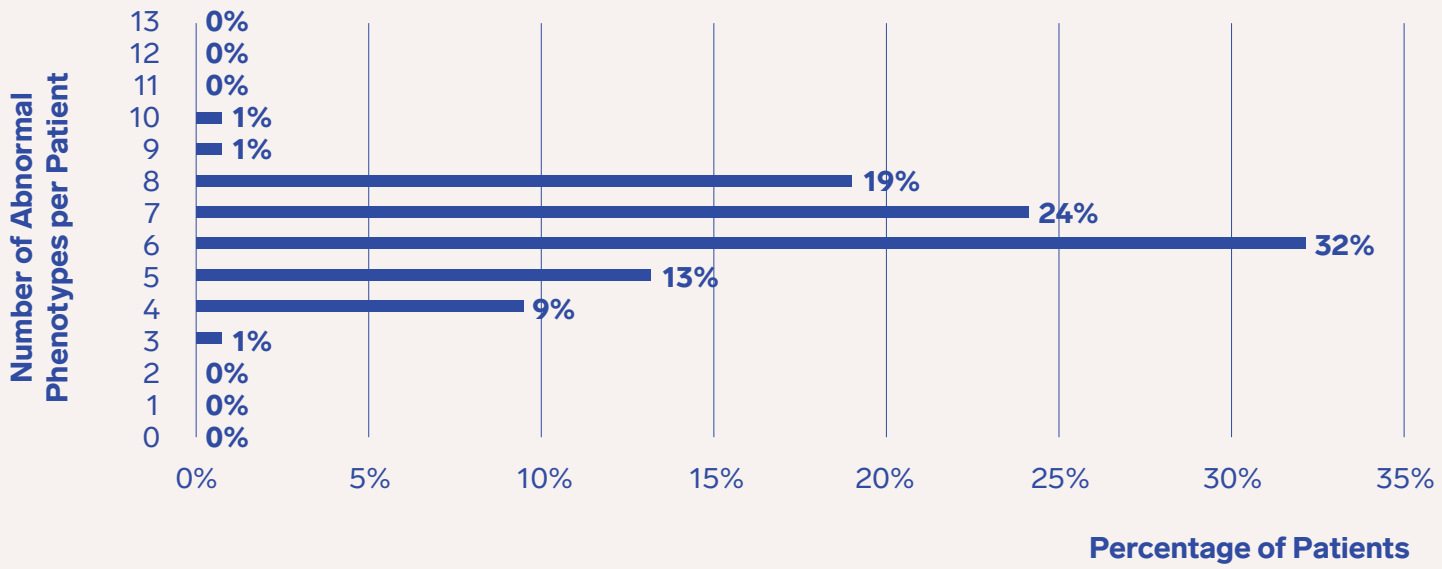

FIGURE 2. Number of abnormal phenotypes per patient for the 13 tested metabolic enzymes (CES1, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, UGT1A1, UGT1A4, UGT2B7, UGT2B15).

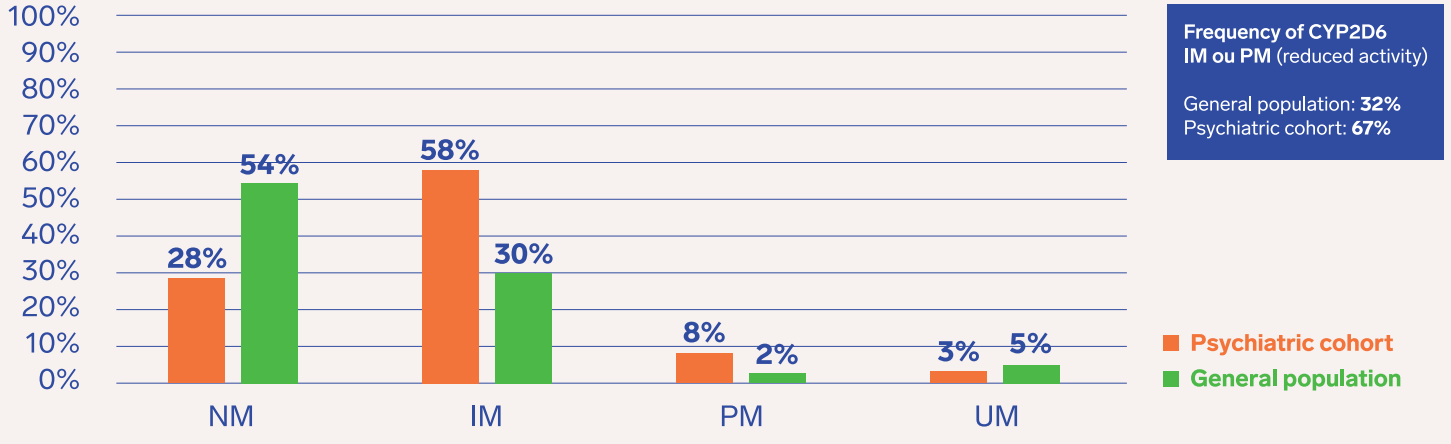

FIGURE 3. Frequency of CYP2D6 phenotypes in psychiatric cohort and general population. Expected phenotype frequencies in the general population were obtained from the « Pharmacogenomics Knowledge Base » website (PGx Gene-specific Information Tables, pharmgkb.org). **NM**: normal metabolizer; **IM**: intermediate metabolizer; **PM**: poor metabolizer; **UM**: ultrarapid metabolizer.

Discussion and Conclusion

This study evaluated the frequency of abnormal metabolizer phenotypes using a pharmacogenomic test in complex psychiatric patients. On average, patients had 6 abnormal phenotypes and the frequency of reduced CYP2D6 activity was 67%, more than twice that observed in the general population. These findings suggest that patients requiring longer periods of trial and error before finding an adequate pharmacological treatment have a higher frequency of genetic variants that can influence drug response, likely contributing to failed pharmacotherapy. This hypothesis is consistent with other studies that have suggested that PGx-guided treatments may provide significant benefits in patients with multiple failed drug trials.[10]

Therefore, using PGx testing in patients with ADHD who do not respond adequately to 1st-line treatments and in patients with ADHD and comorbidities could provide relevant data for physicians deciding on the next course of treatment. Until pre-emptive PGx testing becomes more common, a better understanding of phenotype frequencies across different patient populations will further contribute to identifying patients that can benefit the most from PGx testing. In the meantime, the use of PGx in the clinic could be considered for those patients who are more challenging to treat, with a history of failed pharmacotherapy, as the likelihood of finding clinically significant genetic variants is higher in this group **(Figure 4)**.

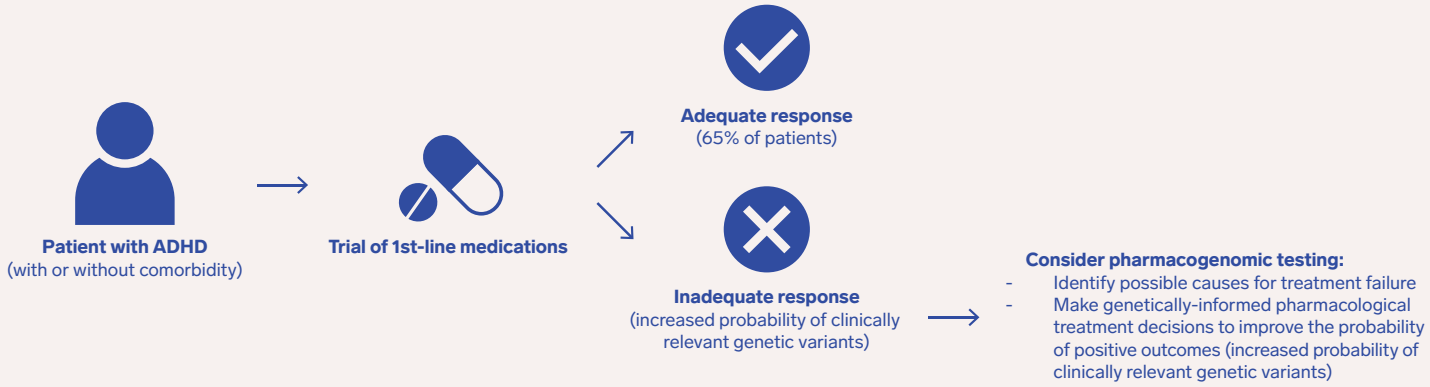

FIGURE 4. Proposed decision algorithm for consideration of pharmacogenomic testing in patients with ADHD.

References

1. Hodgkins P, Shaw M, Coghill D, et al. Amfetamine and methylphenidate medications for attention-deficit/hyperactivity disorder: complementary treatment options. Eur Child Adolesc Psychiatry 2012;21(9):477–92.
2. Su Y, Li H, Chen Y, et al. Remission rate and functional outcomes during a 6-month treatment with osmotic-release oral-system methylphenidate in children with attention-deficit/hyperactivity disorder. J Clin Psychopharmacol 2015;35:525–34.
3. Chou WJ, Chen SJ, Chen YS, et al. Remission in children and adolescents diagnosed with attention-deficit/hyperactivity disorder via an effective and tolerable titration scheme for osmotic release oral system methylphenidate. J Child Adolesc Psychopharmacol 2012;22:215–25.
4. Kessler, R.C., et al., The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry, 2006. 163(4): p. 716-723.
5. Cumyn, L., L. French, and L. Hechtman, Comorbidity in adults with attention-deficit hyperactivity disorder. Can J Psychiatry, 2009. 54(10): p. 673-683.
6. Wooltorton, E., Suicidal ideation among children taking atomoxetine (Strattera). CMAJ, 2005. 173(12): p. 1447.
7. ADHD comorbidity findings from the MTA study: comparing comorbid subgroups. J Am Acad Child Adolesc Psychiatry, 2001. 40(2): p. 147-58.
8. Cascade, E., A.H. Kalali, and R.H. Weisler, Short-acting versus long-acting medications for the treatment of ADHD. Psychiatry (Edgmont), 2008. 5(8): p. 24-27.
9. Faraone, S.V., et al., Comparing the efficacy of medications for ADHD using meta-analysis. MedGenMed, 2006. 8(4): p. 4.
10. Brown JT, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for Cytochrome P450 (CYP)2D6 Genotype and Atomoxetine Therapy. Clin Pharmacol Ther (2019).
11. Bousman CA, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6, CYP2C19, CYP2B6, SLC6A4, and HTR2A Genotypes and Serotonin Reuptake Inhibitor Antidepressants. Clin Pharmacol Ther (2023).
12. Hicks JK, et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther (2017).
13. Dutch Pharmacogenetics Working Group (DPWG) 2021 update (https://api.pharmg-kb.org/v1/download/file/attachment/DPWG_May_2021.pdf).
14. Brown LC et al. Pharmacogenomic Testing and Depressive Symptom Remission: A Systematic Review and Meta-Analysis of Prospective Controlled Clinical Trials. Clin Pharmacol Ther 2022 112(6):1303-1317.
15. Schaars KK and van Westrhenen R. Pharmacogenomics and the Management of Mood Disorders-A Review. J Pers Med (2023) 13(7):1183.
16. Aldrich SL et al. Influence of CYP2C19 Metabolizer Status on Escitalopram/Citalopram Tolerability and Response in Youth With Anxiety and Depressive Disorders. Front Pharmacol (2019) 10:99.
17. Jukic MM et al. Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study. Lancet Psychiatry (2019) 6(5):418-426.
18. Jukic MM et al. Impact of CYP2C19 Genotype on Escitalopram Exposure and Therapeutic Failure: A Retrospective Study Based on 2,087 Patients. Am J Psychiatry (2018) 175(5):463-470.
19. Brown JT et al. Clinical Pharmacogenetics Implementation Consortium Guideline for Cytochrome P450 (CYP)2D6 Genotype and Atomoxetine Therapy. Clin Pharmacol Ther (2019) 106(1):94-102.
20. Hicks JK et al. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update. Clin Pharmacol Ther (2017). 102(1):37-44.
21. Bousman CA et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6, CYP2C19, CYP2B6, SLC6A4, and HTR2A Genotypes and Serotonin Reuptake Inhibitor Antidepressants. Clin Pharmacol Ther (2023) 114(1):51-68.
22. Dutch Pharmacogenetics Working Group (DPWG) 2021 update (https://api.pharmg-kb.org/v1/download/file/attachment/DPWG_May_2021.pdf).