mhc
MENTAL HEALTH CLINICIAN

CASE REPORT Open Access

Using pharmacogenomics and therapeutic drug monitoring to guide drug selection and dosing in outpatient mental health comprehensive medication management

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How to cite: Brown JT, Bishop JR, Schneiderhan ME. Using pharmacogenomics and therapeutic drug monitoring to guide drug selection and dosing in outpatient mental health comprehensive medication management. Ment Health Clin [Internet]. 2020;10(4):254-8. DOI: 10.9740/mhc.2020.07.254.

Abstract

Pharmacogenomic (PGx) testing aided by therapeutic drug monitoring (TDM) has the potential to improve medication-related outcomes in some individuals prescribed psychiatric medications. Many commonly prescribed psychiatric medications are metabolized through polymorphic drug metabolizing enzymes such as cytochrome p450 (CYP) 2D6 (CYP2D6) and CYP2C19. Through PGx testing, clinicians can make biologically informed choices when selecting a new medication, and TDM may help inform dose adjustments or assess exposures to current treatments. Herein, we describe 2 complex case reports of individuals with multiple psychiatric diagnoses and extensive histories of medication failures who underwent PGx testing in addition to TDM as part of a pharmacist-led comprehensive medication therapy management evaluation in a community mental health clinic setting.

Keywords: pharmacogenomics, therapeutic drug monitoring, psychopharmacology, CYP2C19, CYP2D6, comprehensive medication management

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Introduction

Precision therapeutics, in the form of therapeutic drug monitoring (TDM) combined with pharmacogenomic (PGx) testing, has the potential to help some patients struggling with psychiatric illnesses requiring complex pharmacological treatments.[1,2] These patients often have extensive and complicated histories of multiple medication trials and failures. Patients and their providers are often frustrated with the challenge of finding a suitable medication. Pharmacogenomic testing and TDM are currently not standard-of-care approaches to guide drug selection and dosing for many medications used for mental health indications. However, growing evidence suggests that PGx and TDM data may be informative in drug selection or dosing decisions for some patients. Although PGx testing may be useful before a patient is prescribed medications early in therapy, empirical data supporting this practice are lacking, and as a result, preemptive testing is rare. Thus, many patients currently being referred for PGx testing have typically tried and failed multiple medication trials in an attempt to find treatments that are efficacious and tolerable.

Recently updated consensus guidelines for TDM in neuropsychopharmacology (Arbeitsgemeinschaft fur Neu-

ropsychopharmackologie und Pharmakopsychiatrie [AGNP]) provide reference ranges for a number of commonly prescribed psychiatric medications.[3] Although not absolute, these reference ranges provide relevant context for clinicians evaluating patients taking psychiatric medications to determine whether their current drug exposure may be too high (increasing risk for adverse reactions) or too low (limiting effectiveness). Pharmacogenomic testing helps identify which patients with altered hepatic metabolism due to genetic factors may be at risk for adverse effects or lack of therapeutic effect at standard doses.[4]

The combination of TDM with PGx testing may provide clinicians with additional information relevant to medication dose and selection and may be, in certain cases, more useful than either approach alone. Examples of this approach exist for oncology, antitubercular, and antifungal medications.[5-8] For individuals experiencing adverse drug reactions or a lack of medication response, TDM provides clinicians with an objective phenotypic measure of the relative exposure a patient is currently experiencing on that specific dosing regimen. Additionally, this information can help inform to what extent a medication inducer or inhibitor is impacting the serum concentrations of another medication. Finally, TDM can clarify the impact of PGx results that may lack clarity with respect to clinical utility (eg, intermediate metabolizers or rare genotype combinations for which functional status is unclear). Conversely, PGx may provide the clinician with information to help explain previous and current medication experiences in addition to guiding future medication and dose considerations based on a patient's genetic predisposition.

This report contains 2 cases of individuals with multiple psychiatric diagnoses, several medication trials and failures, PGx results, and TDM of select medications. Consistent between the 2 cases are the use of a CYP2C19 substrate antidepressant (escitalopram) and a CYP2D6 antipsychotic (aripiprazole), both of which have US Food and Drug Administration (FDA) labels noting the potential impact of genetically defined drug metabolism phenotypes. The purpose of this report is to describe the potential clinical utility of combining and interpreting PGx and TDM results in a community mental health clinic to educate and guide patient-centered comprehensive medication management (CMM) in complex treatment situations.

Cases

Both cases included within this report were referred to a CMM psychiatric pharmacist (M.E.S.) for consultation and collaborative medication therapy management. Pharmacogenomic test results of each patient can be found in the Table.

TABLE: Pharmacogenomic test results for both cases

Gene	Case 1	Case 2
CYP2C19	*1/*17 – rapid metabolizer	*1/*2 – intermediate metabolizer
CYP2D6	*2A/*4 – normal metabolizer	*3/*4 – poor metabolizer

Case 1

Case 1 is a 46-year-old female with chart diagnoses of moderate-to-major depressive disorder; recurrent, moderate, obsessive-compulsive disorder; generalized anxiety disorder; other unspecified personality disorder with dependent features; and tardive dyskinesia who received ongoing care at the clinic for several years. She was referred by her psychiatrist to consider PGx testing after reporting ineffectiveness and adverse drug reactions to many psychotropic agents over 30 years, including antidepressants, antipsychotics, stimulants, and mood stabilizers. Her history included chronic suicidal ideation and multiple suicide attempts via overdose on venlafaxine, fluoxetine, and loxapine. At the time of her referral, she reported intrusive persecutory and suicidal thoughts, anxiety, and depression causing poor sleep quality and isolation. Additionally, the patient reported tongue swelling, headache, insomnia, and tardive dyskinesia symptoms attributed (per medical records) to loxapine, a CYP2D6, CYP1A2, and CYP3A4 substrate,[9] which had been recently discontinued after a suicide attempt approximately 1 month prior to referral. At the time of referral, patient and provider were considering clozapine therapy to target suicidal ideation; however, she was reluctant to initiate this treatment due to the frequent blood monitoring and preferred to try an alternative treatment. Additionally, the psychiatrist, patient, and family all felt that escitalopram at 40 mg/d was ineffective but were reluctant to make any dose changes. At this point, PGx testing was offered to the patient and family to provide a clearer path to shared decision making. The hope was to address the growing frustration and anxiety verbalized by the patient and her family around these failed medication trials and multiple medication changes. The patient and family agreed and consented to PGx testing, and an escitalopram serum concentration was ordered to provide a better understanding of current drug exposure.

Pharmacogenomic testing identified her as a CYP2C19 rapid metabolizer (rapid metabolizer is the current nomenclature for individuals with a CYP2C19 *1/*17

genotype; thus, they fall between normal and ultrarapid metabolizers) and a CYP3A4 and CYP2D6 normal metabolizer. The escitalopram trough serum concentration ordered when she was taking 40 mg/d (twice the maximum recommended daily dose) was reported as 38 ng/mL (AGNP therapeutic reference range: 15 to 80 ng/mL). Although within the AGNP therapeutic range, based upon a lack of clinical response at high doses, concern for increasing the dose further beyond twice the maximum recommended, and discussion with the patient and her family, it was decided to discontinue escitalopram and switch to levomilnacipran, a serotonin/norepinephrine reuptake inhibitor and CYP3A4 substrate. Furthermore, based on her reluctance to try clozapine, she accepted a plan to start cariprazine (a CYP3A4 substrate) after review of PGx results indicated her CYP3A4 normal metabolizer status.

The patient's medication history was notable for previous trials to several other CYP2C19 substrates (eg, amitriptyline, citalopram, clomipramine, and sertraline). At standard doses, CYP2C19 rapid or ultrarapid metabolizer status would increase the likelihood of inadequate exposure and nonresponse. According to the Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines, if CYP2C19 rapid metabolizer status is known *prior to* drug selection, recommendations include considering avoiding escitalopram or citalopram.[10] Considering PGx alone, this pattern of prior nonresponse might be exclusively attributed to metabolism. Knowing genotype information suggests that dosing of CYP2C19 substrates moving forward may be complicated by her rapid metabolizer status, which may necessitate higher than usual dosing for CYP2C19 substrate medications or choosing a drug not metabolized by CYP2C19. The normal CYP2D6 and CYP3A4 results provided important information that helped to rule out metabolic PGx contributors to some previously experienced antipsychotic side effects. This information was helpful in considering subsequent antipsychotic options and engaging the patient and family in the decision-making process. The patient has not had any further hospitalizations for overdose attempts since PGx/TDM testing and CMM consultation.

Case 1 Summary

Pharmacogenomic test results identified the patient as a CYP2C19 rapid metabolizer relevant to current and previous antidepressants, ruled out metabolic PGx contributions to antipsychotic side effects, and enhanced patient engagement with the shared therapeutic decision-making process. Therapeutic drug monitoring verified that the supratherapeutic dose achieved adequate exposure to the antidepressant in a genetic rapid metabolizer to rule out inadequate exposure as a reason for nonresponse. Although inadequate exposure was ruled out, it remains to be determined whether the cost of TDM is justified by this additional clinical data point in such cases. Together, PGx and TDM informed the decision to switch antidepressant class and guided specific drug selection to avoid future metabolic confounders.

Case 2

Case 2 is a 68-year-old female historically resistant to medication switches and dose reductions with chart diagnoses of bipolar I disorder in partial remission (most recent episode depressed), posttraumatic stress disorder (unspecified), attention deficit/hyperactivity disorder, anorexia nervosa (restricting type), borderline personality disorder, and mild opioid use disorder (postsurgery). Although currently not active problems, her past history of suicide attempts, substance use (alcohol, methamphetamines, psilocybin), and self-injurious behaviors since high school added complexity to her pharmacotherapy management history. She was referred to the CMM pharmacist for PGx testing and medication assessment due to ineffective drug therapy, her multiple requests for additional medications, dose increase requests, and suspected akathisia from aripiprazole along with several related or potentially contributing factors (eg, insomnia, restless leg syndrome, irritability). After PGx testing results were obtained, serum concentrations were also ordered for escitalopram, duloxetine, and aripiprazole to help determine if any notable deviations from expected exposure ranges might have been contributing to ineffectiveness and side effects.

Her PGx test results identified her as an intermediate metabolizer (ie, more activity than a poor metabolizer but less activity than a normal metabolizer) for CYP2C19 and a poor metabolizer for CYP2D6. Reduced (poor or intermediate metabolizer status) activity of both of these drug-metabolizing enzymes could have contributed to her lack of symptom improvement and adverse effects to several previously trialed psychiatric medications. Her escitalopram serum concentration at 30 mg/d was reported as 97 ng/mL (above the AGNP reference range of 15 to 80 ng/mL), which may be, in part, explained by her intermediate CYP2C19 metabolism. Her duloxetine serum concentration at 90 mg/d was within the normal AGNP reference range at 114 ng/mL (30 to 120 ng/mL). Finally, her aripiprazole and dehydroaripiprazole serum concentrations at 30 mg/d were reported as 342.8 ng/mL (therapeutic reference range: 100 to 350 ng/mL) and 68.3 ng/mL for a total of 411.1 ng/mL (therapeutic reference range: 150 to 500 ng/mL). Of note, duloxetine is also a substrate of CYP1A2 and aripiprazole a substrate of CYP3A4, which may also contribute to these results. Although duloxetine is an inhibitor of CYP2D6, this is not expected to further decrease metabolic activity in a genetically determined poor metabolizer.

The CMM pharmacist provided an explanation of PGx and TDM findings and recommendations. Based on this individual's CYP2D6 poor metabolizer status and adverse effect profile, the patient subsequently agreed to a dose reduction of aripiprazole after solidly resisting previous recommendations to decrease her dose. Initial dose reductions did not worsen depressive/anxiety symptoms, but there was an improvement of akathisia.

Case 2 Summary

Pharmacogenomics identified this patient as a CYP2C19 intermediate metabolizer and a CYP2D6 poor metabolizer, which were relevant to 2 antidepressants and 1 antipsychotic used by the patient at the time of referral. Pharmacogenomics enhanced patient engagement with the shared therapeutic decision-making process and facilitated dose reductions that improved dose-related side effects without worsening symptoms. Therapeutic drug monitoring verified that escitalopram (CYP2C19 substrate) exposure was high and that aripiprazole (a CYP2D6 substrate) exposure was at the higher end of the therapeutic range. Together, PGx and TDM clarified exposure of current antidepressants and the antipsychotic and collectively facilitated patient engagement with dose reductions to improve side effects.

Discussion

In both of the cases presented herein, PGx testing along with TDM provided clinicians and patients with relevant information to help educate and guide the subsequent medication selection and dosing strategies in situations in which most options had been exhausted. In these patients, PGx testing was useful in three ways: (1) it helped to explain (in part) their previous medication failures or intolerance; (2) it guided future drug selection; and (3) it improved patient engagement with therapy to formulate patient-centered medication treatment plans. Additionally, each of these individuals had either increased or decreased function of CYP2D6, CYP2C19, or both and had either previously been prescribed or were presently taking several medications impacted by these enzymes. Therapeutic drug monitoring was helpful to clarify current drug exposure in the context of different combinations of non-normal metabolizer genotypes alongside drug doses that were within or above doses listed in the FDA labels.

Pharmacogenomic information is increasingly being included in FDA labeling. Several medications now include dose recommendations based on metabolizer status. For example, aripiprazole contains dosing recommendations that, in CYP2D6 poor metabolizers (as was the result in case 2), 50% of the recommended starting dose be prescribed.[11] The labeling for escitalopram notes that CYP2C19 poor metabolizer status confers supratherapeutic doses.[12] Additionally, the CPIC provides dosing recommendations for a number of psychiatric medications based on *CYP2D6* (eg, paroxetine, fluvoxamine, and atomoxetine) and *CYP2C19* (citalopram/escitalopram and sertraline) genotypes.[10,13] At the present time, the CPIC has not conducted a guideline review for antipsychotic agents, but the Dutch Pharmacogenetics Working Group has and suggests dose adjustments based on CYP2D6 genetic metabolizer status.[14]

Although PGx testing and TDM are not currently standard of practice, case reports can demonstrate the clinical utility of combining PGx testing with TDM to navigate complex psychotropic medication therapy for some patients.[15] It is important to note the limitations of PGx and TDM in clinical practice and the cases presented here. Although data are increasing our confidence in the clinical relevance of some PGx associations, many currently available commercial tests contain information for more genes than those referenced in FDA product labeling or CPIC guidelines, necessitating that providers become knowledgeable about the clinical relevance of test results. Additionally, our understanding of which patients may benefit most from this type of testing and when it is best obtained (eg, at what time in the treatment course it should be obtained) is incomplete. In the patients reported herein, this process facilitated patient engagement with therapeutic decision making although it is unclear whether this was related to specific clinical characteristics (eg, extensive medication histories, multiple diagnoses, personality traits, etc). Personality traits, personality disorders, and substance use are known to reduce responsiveness to some pharmacologic treatments and may complicate the interpretation of genotype and drug exposure data, which have primarily been studied in patients without these characteristics. Although some psychiatric medications have well-described therapeutic ranges (eg, tricyclic antidepressants), others lack precise guidance. For antidepressants or antipsychotics with known dose relationships with response or tolerability, broadly knowing whether drug exposure is present or absent or lower or higher than reference ranges may be informative.[16,17] The AGNP guidelines are helpful in providing the clinical relevance of therapeutic ranges by assigning levels of recommendation ranging from strongly recommended to potentially useful. Last, the cost of PGx and TDM must be considered when ordering such testing for patients. Of note, a major health care insurance company recently announced coverage of pharmacogenetic testing for (1) individuals with a diagnosis of major depressive disorder or anxiety; (2) if the patient has failed at least 1 prior medication; and (3) the gene panel ordered has no more than 15 relevant genes.[18] Still, the cost or

uncertainty of coverage of PGx testing may still be a barrier for some patients.

Conclusion

Patients with multiple psychiatric and comorbid diagnoses frequently undergo medication trials with varying success. Pharmacogenomics can help clinicians in assessing historical, current, and future medication considerations, and TDM allows for informed dose adjustments based on current drug exposure and to clarify the relevance of unclear PGx results. This process also may enhance patient engagement with medication therapy and facilitate needed changes. With PGx and TDM, clinicians can apply informed decision-making processes to improve patients' confidence and acceptance of their current and future medication treatment plans. Improving our understanding of which patients may benefit most from PGx and TDM will facilitate best practices of how and when to integrate these data into routine clinical care.

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