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CASE REPORT

Utilizing Pharmacogenomics Results to Determine Opioid Appropriateness and Improve Pain Management in a Patient with Osteoarthritis

Katie Pizzolato[1], David Thacker[2], Nicole Marie Del Toro-Pagán[1], Nishita S Amin[1], Abeer Hanna[3], Jacques Turgeon[2,4], Veronique Michaud[2,4,5]

[1]Tabula Rasa Healthcare, Office of Translational Research and Residency Programs, Moorestown, NJ, 08057, USA; [2]Tabula Rasa HealthCare, Precision Pharmacotherapy Research and Development Institute, Orlando, FL, 32827, USA; [3]VieCare Butler, Program of All-Inclusive Care for the Elderly (PACE), Butler, PA, 16001, USA; [4]Faculty of Pharmacy, Université de Montréal, Montréal, QC, H2L, Canada; [5]University of Montreal Hospital Research Center (CRCHUM), Montréal, QC, H2X 0A9, Canada

Correspondence: Veronique Michaud, Precision Pharmacotherapy Research and Development Institute, 13485 Veterans Way, Orlando, FL, 32827, USA, Tel +856-938-8697, Email vmichaud@trhc.com

Abstract: The opioid epidemic in the United States has exposed the need for providers to limit opioid dispensing and identify at-risk patients prior to prescribing opioids. With pharmacogenomic testing, clinicians can analyze hundreds of medications—including commonly prescribed opioids—against genetic results to understand and predict risk and response. Moreover, knowledge of genotypic variants and altered function can help decrease trial and error prescribing, identify patients at-risk for adverse drug events, and improve pain control. This patient case demonstrates how pharmacogenomic test results identified drug–gene interactions and provided insight about a patient's inadequate opioid therapy response. With pharmacogenomic information, the patient's healthcare team discontinued opioid therapy and selected a more appropriate regimen for osteoarthritis (ie, celecoxib), resulting in improved pain control and quality of life.

Keywords: CYP2D6, CYP2C9, drug–gene interactions, opioids, pain management, pharmacogenomics

Introduction to Patient Case

A 69-year-old patient with polypharmacy and comorbidities presented to her provider with complaints of severe back and knee osteoarthritis pain after failing to achieve adequate relief with tramadol and oxycodone. A pharmacogenomic test was completed to identify underlying genetic variants that may be leading to inadequate pain control.

Introduction

Pain management and its subjectivity pose a unique challenge for clinicians, especially in older patients with multiple comorbidities. For example, while non-steroidal anti-inflammatory drugs (NSAIDs) are first-line treatment for osteoarthritis, they may not be preferred in patients with cardiovascular disease history.[1,2] Pain management is more complicated with opioids and providers must be critical when determining the appropriate patients to receive opioids. Providers must incorporate ways to improve medication safety, establish optimal pain regimens, and determine opioid appropriateness.[3]

Individual response to opioids depends on several factors (eg, genetics, age, comorbidities, concomitant medications). Utilizing personalized medicine can improve medication safety and help pinpoint patients who are at risk for side effects and pharmacotherapy failure.[4] Pharmacogenomic (PGx) testing is one tool to help individualize therapy, as PGx information reveals the extent to which gene and subsequent enzyme function may lead to pharmacokinetic or pharmacodynamic changes. These changes can result in increased risk for opioid-related adverse drug events (ADEs), such as respiratory depression and/or pharmacotherapy failure.[5,6] Several studies and healthcare settings have observed improvement in pain management with PGx integration and recognized individualized therapy promotes medication

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safety.[3,6] Furthermore, PGx results provide objective information to facilitate conversations between healthcare providers and patients about why opioid therapy may or may not be safe and/or appropriate.[7,8]

Problems with drug–gene interactions (DGIs) have been well established for analgesics, such as with cytochrome P450 (*CYP)2D6* and certain opioids (eg, codeine, tramadol, oxycodone, hydrocodone). DGIs related to *CYP2C9* and NSAIDs, such as ibuprofen and celecoxib, have also been extensively studied.[9–11] Incorporating PGx results into clinical decision-making decreases medication trial and error, potentially reducing time needed to achieve successful therapy and exposure to inappropriate medications.[9,10] This patient case demonstrates how PGx-informed clinical decision-making optimizes pain management and improves patient outcomes by determining opioid appropriateness.

Case Presentation

A 69-year-old female patient with multiple comorbidities and prescribed medications (Table 1) presented to her provider struggling to walk and experiencing unbearable knee and back pain, primarily due to chronic osteoarthritis. The patient was deemed ineligible for NSAID therapy and was prescribed tramadol 50mg more than three years ago for osteoarthritis pain. Tramadol initially provided analgesia, but over time, the patient reported needing tramadol more frequently for pain relief. At the most recent physician visit, the patient rated her pain as severe, with a 10/10 on the numeric rating scale (NRS), despite taking tramadol 50mg four times a day and acetaminophen as needed. The provider discontinued tramadol and prescribed oxycodone 5mg three times per day, instructing the patient to follow up in a few days. The patient experienced some improvement with oxycodone (6/10 NRS). In collaboration with the healthcare team, a PGx test was recommended, and a clinical pharmacist was then consulted to conduct a medication review.

The clinical pharmacist assessed the patient's medication regimen using a clinical decision support system (Figure 1) following the results of the PGx test (Table 2), which was analyzed and interpreted by an external PGx vendor, OneOme®.[12] The patient was found to be a CYP2D6 intermediate metabolizer (IM) based on the *CYP2D6* genotype results (**9|*41*).[9] CYP2D6 IMs are expected to have an increased risk for pharmacotherapy failure with CYP2D6-activated opioids (eg, tramadol, oxycodone) due to reduced transformation of opioids into their more active metabolites (eg, O-desmethyltramadol, oxymorphone).[9,11] At CYP3A4, drug–drug interactions (DDIs) of competitive inhibition of

Table 1 Current Patient's Medication List at the Time of PGx Testing

Condition	Medication	Dose	Frequency	Route of Administration
Coronary artery disease	Apixaban	5mg	Twice daily	Orally
Constipation	Docusate	100mg	Twice daily	Orally
Hyperlipidemia	Atorvastatin	20mg	At bedtime	Orally
Hypertension	Amlodipine	5mg	Every morning	Orally
	Furosemide	20mg	Every morning	Orally
Insomnia	Melatonin	3mg	Nightly	Orally
Major depressive disorder	Sertraline	200mg	At bedtime	Orally
Osteoarthritis	Acetaminophen	1300mg	Three times daily as needed for pain	Orally
	Diclofenac	0.3% (2g)	Twice daily to both knees as needed for pain	Topically
	Oxycodone	5mg	Three times a day	Orally
Seasonal allergies	Cetirizine	5mg	Daily	Orally

Abbreviation: PGx, Pharmacogenomics.

Substance	CYP1A2	CYP2B6	CYP2C19	CYP2D6	CYP3A4
Morning					
Amlodipine					
Apixaban					
Oxycodone				‡	
Evening					
Apixaban					
Oxycodone				‡	
Bedtime					
Atorvastatin					
Cetirizine					
Melatonin					
Oxycodone				‡	
Sertraline					
As needed					
Acetaminophen					

Figure 1 Summary of CYP450 affinity and metabolic pathways of patient's medication regimen prior to PGx testing.
Notes: †Only CYP-metabolized oral medications are displayed. ‡Prodrug. Figure adapted from the clinical-decision support system, MedWise®: it shows substances with their differing metabolic pathways and their affinities for the CYP450 isoform (eg, light yellow = weak affinity, dark yellow = moderate affinity).

Weak Substrate	Moderate Substrate

Abbreviations: CYP, cytochrome P450; PGx, pharmacogenomics.

oxycodone perpetrated by coadministration of atorvastatin and amlodipine were identified.[13–15] These interactions cause increased plasma concentrations of parent drug, oxycodone, which may result in increased risk for ADEs (eg, constipation, nausea). This case report focuses on medications involved in pain management; however, a summary of the clinical pharmacist's comprehensive recommendations is in Table 3.

Given the limited success observed with opioid therapy, the pharmacist evaluated alternative analgesics based on the patient's pain indication (ie, osteoarthritis), comorbidities, concomitant medications, renal clearance (ie, 66 mL/min), and PGx results. Celecoxib, a COX-2 inhibitor NSAID, is a first-line medication for osteoarthritis and is not metabolized by CYP2D6.[16] The clinical pharmacist identified a DGI with *CYP2C9* and celecoxib. As a CYP2C9 IM, the patient had an increased risk for celecoxib-related ADEs (eg, altered kidney function, hypertension).[17] However, PGx guidelines do not indicate the medication should be avoided.[17] The clinical pharmacist recommended discontinuing oxycodone, prescribing celecoxib 100 mg twice a day, and monitoring for efficacy and ADEs.

Table 2 Patient's PGx Results

Gene	Result	Phenotype
CYP2B6	*1|*6	Intermediate metabolizer
CYP2C9	*1|*2	Intermediate metabolizer
CYP2C19	*1|*17	Rapid metabolizer
CYP2D6	*9|*41	Intermediate metabolizer
‡*CYP3A4*	*1|*1	Undetermined
CYP3A5	*3|*3	Non-expresser

Notes: ‡*CYP3A4* gene shows some genetic variations and most variants have not been demonstrated to clinically alter the activity of CYP3A4. Many of the variants are extremely rare, making it difficult to derive a phenotype based on genetic results.[31]

Abbreviations: CYP, cytochrome P450; PGx, pharmacogenomics.

Recommendations were communicated to the provider and, with patient acceptance, were implemented. During the two-week follow-up, the patient reported success with celecoxib and continued use of topical diclofenac, experiencing no pain (0/10 NRS). The patient also reported an improved quality of life, regaining the ability to walk long distances without pain.

Discussion

Some of the most prescribed opioids (eg, tramadol, oxycodone, hydrocodone) require activation by CYP2D6 to provide adequate pain relief.[9,11] In this case, PGx results revealed that the patient is a CYP2D6 IM, explaining why treatment with tramadol 50mg up to 4 times a day for chronic back and knee pain provided almost no pain relief (NRS 10/10, severe pain).

Tramadol is federally listed as a schedule IV-controlled substance; most opioids which are schedule II. Approximately 50% of tramadol undergoes metabolism in the liver via the CYP2D6 enzyme to transform into its active metabolite, O-desmethyltramadol (M1).[18,19] O-desmethyltramadol is primarily responsible for analgesic effect, as it has a 200 times greater affinity for the mu-opioid receptor than tramadol.[20,21] Although tramadol itself is metabolically active, it exerts more significant effects on serotonin and norepinephrine uptake.[20]

As a CYP2D6 IM, this patient has less enzyme function compared to normal metabolizers (NMs).[22] This patient's decreased capability to metabolize tramadol resulted in lower plasma concentrations of O-desmethyltramadol and, therefore an increased risk for pharmacotherapy failure.[22] Additionally, this resulted in increased plasma concentrations of tramadol, increasing the risk for serotonergic ADEs.[20,22] The increased exposure to serotonergic properties is an equally important risk, as this patient was also prescribed sertraline 200mg daily, further increasing the risk for side effects associated with serotonin load.[20,21]

Oxycodone was prescribed as an alternative opioid after therapy failure with tramadol. Oxycodone also requires CYP2D6 enzyme activity, and only ~10% of the parent drug is transformed into the more potent, active metabolite, oxymorphone.[23,24] Oxymorphone affinity for mu-receptors is 60 times higher than oxycodone, but both oxycodone and oxymorphone bind to and activate mu-receptors to provide analgesic effects.[9,25]

There are limited PGx recommendations regarding CYP2D6 and oxycodone.[9,26] Several studies have demonstrated a positive correlation between oxycodone efficacy and oxymorphone concentrations.[11,27] These studies demonstrated pharmacokinetics differences in CYP2D6 IMs compared to NMs. IMs are at risk of nonoptimal pain control due to their decreased enzyme function, resulting in lower concentrations of the more active metabolite.[11] Furthermore, DDIs identified at CYP3A4 affected oxycodone due to coadministration of competitive substrate inhibitors (atorvastatin and amlodipine).[13–15] Approximately 30% of oxycodone is metabolized via CYP3A4 to a non-active metabolite, noroxycodone; however, competitive inhibition could lead to increased plasma concentrations of oxycodone and an increased risk for ADEs (eg, constipation, nausea).[24,28,29] Parent drug oxycodone provides partial analgesic effects, and the patient's slight improvement in pain with oxycodone (NRS 6/10)—as opposed to with tramadol—aligns with available data regarding their pharmacological effects.[11,23] However, oxycodone did not provide adequate pain control, and the provider and patient accepted the primary recommendation to discontinue opioid therapy.

To optimize the patient's pain control, the clinical pharmacist applied the PGx results to potential alternatives. Celecoxib was the best option given the indication for osteoarthritis, high COX-2 selectivity, and lower risk for gastrointestinal issues compared to other NSAIDs (eg, ibuprofen, naproxen).[16] Regarding PGx results, PGx-focused guideline recommendations for NSAIDs and

CYP2C9 suggest initiating therapy with the lowest recommended dose and carefully monitoring for hypertension and altered kidney function.[17] While NSAIDs are first-line therapy for osteoarthritis, they should be used carefully in older adults, as the presence of certain comorbidities (eg, heart failure with reduced ejection fraction) and/or decreased renal function increases the risk for other complications.[2] In this case, the patient had controlled hypertension (last measurement 120/70 mmHg) and stable renal function; nonetheless, the importance of monitoring was further emphasized.[30] Lastly, while DGIs and DDIs affecting this patient's analgesics were discussed in detail, other drug interactions were identified by the clinical pharmacist in the comprehensive review, including DGIs with *CYP2C19* and sertraline and melatonin. Several recommendations were accepted to mitigate interactions identified by the pharmacist (Table 3).

For those suffering from osteoarthritis pain, especially in the knees, it is common to observe a decline in mobility and ability to complete daily tasks.[1] The discontinuation of oxycodone and initiation of celecoxib resulted in positive patient outcomes, supported by the patient's perceived decrease in pain score to 0 (no pain) when using celecoxib and topical diclofenac for pain management. Furthermore, patient-reported improvement in the distance able to walk reflects improved pain and quality of life. After two weeks of therapy with celecoxib, the patient's blood pressure and renal function remained stable.

Conclusions

Integrating PGx results into patient care and pain management continues to expand and demonstrate its value by identifying patients at risk for serious medication-related ADEs and who may not benefit from therapy. This patient case highlights how PGx-informed medication review improves pain management, provides explanatory evidence regarding inadequate opioid response, and helps reduce the overutilization of opioids.

Table 3 Pharmacist-Led Comprehensive Review for the Patient and Prescriber Response

Medication(s)	Rationale	Recommendation	Prescriber Response
Oxycodone 5mg three times a day	• Individuals with CYP2D6 IM status have decreased enzyme activity and will not activate oxycodone as extensively, resulting in higher plasma concentrations of oxycodone but lower concentrations of its active metabolite(s), increasing the risk for pharmacotherapy failure. • Additionally, when oxycodone is given concomitantly with amlodipine or atorvastatin, these drugs are expected to competitively inhibit the CYP3A4 metabolism of oxycodone, further increasing the risk of toxicity. CPIC guidelines do not currently provide guidance, it is worth considering alternative therapy in the event of insufficient response and/or ADEs when other mitigation options have been attempted. • Patient reports oxycodone is working better than tramadol did but is still having pain all the time. NSAIDs, specifically COX-2 inhibitors, such as celecoxib can better contribute to relieve pain caused by osteoarthritis. Celecoxib is impacted by a DGI (CYP2C9 IM), but CPIC guidelines recommend initiating therapy with recommended starting dose and to use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.	• Consider re-evaluating benefit versus risk of continued oxycodone therapy and, as appropriate, consider switching to celecoxib at 100 mg twice daily, which may be more efficacious for osteoarthritis pain. • Alternatively, if opioid use is warranted, separate the timing of administration of oxycodone by at least 2–4 hours from atorvastatin and amlodipine, if possible. Should the response be deemed insufficient, or toxicity is reported, switching to morphine (non-CYP2D6 opioid) can be considered.	• Discontinuing oxycodone and initiating celecoxib 100 mg twice a day. • Will closely monitor blood pressure and renal function.

(*Continued*)

Table 3 (Continued).

Medication(s)	Rationale	Recommendation	Prescriber Response
Apixaban 5mg twice a day Cetirizine 5mg daily	• Patient is taking amlodipine and atorvastatin, drugs that have a stronger affinity for CYP3A4 than apixaban and cetirizine (ie, victim drugs). • Metabolism of the victim drugs will be inhibited when taken at or around the same time of day than amlodipine and atorvastatin. Although the net result cannot be fully determined, when these interactions occur, the plasma concentrations of apixaban and cetirizine will be higher than predicted. As a result, the risk for toxicity may increase. As a result, the participant should be monitored for the following: 1. apixaban – bleeding 2. cetirizine – drowsiness, fatigue • Separating the time of administration may mitigate these interactions.	• Separate the timing of administration of apixaban and cetirizine, by at least 2–4 hours from amlodipine and atorvastatin, if possible. • Consider changing the time of administration of amlodipine from morning to bedtime, to separate from apixaban.	• Will administer amlodipine and atorvastatin at bedtime separated from apixaban. • Cetirizine will be discontinued.
Cetirizine 5mg daily	• Cetirizine has mild anticholinergic properties and adverse event reporting data indicates that nearly 15% of people that take cetirizine can experience drowsiness. Fexofenadine is not metabolized by the P450 system and does not carry appreciable anticholinergic properties. Among the non-sedating antihistamines, fexofenadine has been classified into "non-brain-penetrating antihistamines" based on the brain H1 receptor occupancy studies. When directly compared, patients taking fexofenadine tended to have less psychomotor impairment and sedation.	• Consider changing cetirizine to fexofenadine, given lower potential for DDIs and anticholinergic effects.	• Discontinued cetirizine as there is no need for daily allergy medication.
Melatonin 3mg at bedtime	• Individuals with CYP2C19 RM status have increased enzyme activity compared to normal metabolizers. This will result in lower plasma concentrations of melatonin, increasing the risk for pharmacotherapy failure.	• Consider increasing melatonin dose to 5mg, if difficulty sleeping is reported by patient, given the present DGI.	• Discontinued melatonin as pt is now sleeping without medication.
Sertraline 200mg	• Individuals with CYP2C19 RM status have increased enzyme activity compared to normal metabolizers. This will result in lower plasma concentrations of sertraline, increasing the risk for pharmacotherapy failure. • Per chart, the patient is stable on sertraline (2/5/2021) and mood has improved.	• Continue to closely monitor the effectiveness of sertraline (ie, improved mood). • Consider changing the time of administration from bedtime to morning, given sertraline stimulating properties.	• Will continue to monitor for improved mood and continue sertraline.

Abbreviations: CPIC, Clinical Pharmacogenetics Implementation Consortium; CYP, cytochrome P450; DDI, drug–drug interaction; DGI, drug–gene interaction; IM, intermediate metabolizer; NSAIDs, non-steroidal anti-inflammatory drugs; PGx, pharmacogenomics; RM, rapid metabolizer.

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Ethics Statement

This material has not been previously published elsewhere and is the authors' own work. The paper is not under consideration for publication at another journal. The research in this manuscript was conducted under Study ID: 22-12-045-427 at BRANY IRB, New York, USA. Informed consent was provided by the patient for publication of this case report. This case report was approved for publication by Tabula Rasa HealthCare's Disclosure Committee and Scientific Review Committee. Figures in this manuscript do not require copyright permission from Tabula Rasa HealthCare.

Disclosure

KP, DT, NDTP, NSA, JT, and VM are all employees and shareholders of Tabula Rasa Healthcare. VM and JT report a patent 11364856 issued to TRHC, a patent 10890577 issued to TRHC. The authors report no other conflicts of interest in this work.

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