Integrating Pharmacogenomic Results and Drug-Induced Phenoconversion Concepts while Conducting a Medication Safety Review Process

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Abstract

Opioid appropriateness is primarily focused on insufficient pain control; however, opioid-related adverse drug events (ADE) have also been associated with a negative impact on disability, mood, and quality of life. As progress is made toward determining more appropriate parameters for opioid prescribing, clinicians are beginning to rely on pharmacogenomics (PGx). PGx results can provide valuable patient-specific information about risk for opioid-related ADEs and/or pharmacotherapy failure. The clinical utility of PGx has been associated with limitations; however, considering drug-induced phenoconversion can be a strategy to address limitations in patients with complex drug regimens. This case highlights the importance of considering drug-induced phenoconversion when implementing PGx into clinical practice. This case describes a wheelchair-bound patient who experienced intolerable drowsiness due to oxycodone which was unsuccessful in relieving trigeminal neuralgia-related pain. A clinical pharmacist performed a PGx-informed medication safety review and identified drug interactions causing competitive inhibition of CYP3A4 and drug-drug-gene interactions and drug-induced phenoconversion for CYP2D6 – all of which affected oxycodone metabolism into oxymorphone. This resulted in an increased risk for oxycodone-related ADEs and decreased efficacy. The pharmacist recommended oxycodone discontinuation, optimization of gabapentin, awareness for alternative therapy based on HLA-A PGx results, and patient counseling. Pursuant to therapy changes, the patient experienced better pain control and less drowsiness, which improved her quality of life. This report demonstrates how a PGx-informed medication safety review that assessed drug-drug and drug-drug-gene interactions resulted in better pain management, elimination of opioid-related ADEs, and improved quality of life.
Keywords: CYP2D6; Drug-drug interactions; Drug-drug-gene interactions; Opioids; Oxycodone; Pharmacogenomics; Phenoconversion

Abbreviations: ADEs: adverse drug events, CYP: cytochrome P450, DDI: drug-drug interaction, DDGI: drug-drug-gene interaction, DGI: drug-gene interaction, HLA: human leukocyte antigen, IM: intermediate metabolizer, NM: normal metabolizer, NRS: numeric rating scale, PD: pharmacodynamics, PK: pharmacokinetics, PGx: pharmacogenomics, PM: poor metabolizer, TGN: trigeminal neuralgia

Introduction

The number of opioids prescriptions for pain treatment in the United States in 2011 was 219 million [1,2]. Fortunately, opioid prescriptions have steadily declined to 142 million in 2020 [1]. The belief that opioids are one of the best therapeutic approaches for pain management inhibits further decline. Opioids are not appropriate for all patients and complete pain relief is unattainable for many people. Several factors affect patient response to opioids and should be considered when assessing opioid appropriateness [3]. Pharmacokinetic (PK) and pharmacodynamic (PD) factors contribute to the inter-subject variability observed in opioid response, especially for opioid prodrugs that are bioactivated by the cytochrome (CYP) 2D6 isoenzyme to produce more potent analgesic metabolites (e.g., codeine, tramadol, oxycodone) [4,5]. Administration of other medications with CYP2D6-activated opioids can result in PK or PD interactions, potentially increasing the risk for opioid-related adverse drug events (ADEs) and/or pharmacotherapy failure [4,6]. Given the polymorphic nature of CYP2D6 and the opioid mu receptor, it is assumed that significant variation in PK or PD exists among patients taking opioids. Accordingly, PGx studies have shown correlation with interindividual differences regarding opioid effectiveness [7,8].

Several genetic testing companies have developed PGx panels to help clinicians address inter-subject variability in opioid response; however, the clinical utility of PGx testing has been somewhat controversial in a “real-world setting”. Complexities and limitations arise when interpreting PGx results for patients taking multiple medications that can alter the genotype-predicted phenotype this phenomenon is known as drug-induced phenoconversion [5,9]. Access to clinical decision support systems (CDSS) that integrate a patient’s medication regimen and PGx results can help pharmacists identify and mitigate medication-related problems (e.g., drug-induced phenoconversion) by incorporating these factors into a medication safety review [10-12].

Case Report

73-year-old female patient with multiple comorbidities (Table 1) and a partial left leg amputation presented to her provider for a routine visit. She had a history of chronic neuropathic pain treated with gabapentin and oxycodone/acetaminophen. The patient’s primary complaint was excessive daytime sedation, which was heavily affecting her quality of life. She recently reported experiencing shock-like pains on the right side of the face often triggered by eating breakfast or brushing her teeth in the morning. The provider identified that the patient’s symptoms were due to trigeminal neuralgia (TGN). Pain appeared uncontrolled to a satisfactory level despite already taking pain medication, including oxycodone/acetaminophen 1-2 times daily. The patient reported her pain to be a 5 out of 10 on average using a numeric rating scale (NRS). A PGx test was proposed to help optimize patient’s therapy.
Table 1: Current patient’s medication list at the time of PGx testing.

| Condition                        | Medication         | Dose       | Frequency              | Route of administration |
|----------------------------------|--------------------|------------|------------------------|-------------------------|
| Constipation                     | Docusate           | 100mg      | Twice daily            | Orally                  |
| Gastrointestinal reflux disease  | Pantoprazole       | 40mg       | Daily                  | Orally                  |
| Hyperlipidemia                   | Atorvastatin       | 20mg       | Nightly                | Orally                  |
| Hypertension                     | Amlodipine         | 2.5mg      | Nightly                | Orally                  |
| Insomnia                         | Melatonin          | 3mg        | Nightly                | Orally                  |
| Iron deficiency                  | Ferrous sulfate    | 325mg      | Twice daily            | Orally                  |
| Major depressive disorder        | Duloxetine         | 60mg       | Daily                  | Orally                  |
| Neuropathic pain                 | Acetaminophen      | 325mg      | Three times daily as needed for pain | Orally                  |
|                                  | Gabapentin         | 100mg      | Three times a day      | Orally                  |
|                                  | Oxycodone/ acetaminophen | 5/325mg | One-two times a day as needed for pain | Orally                  |
| Peripheral artery disease        | Aspirin            | 81mg       | Daily                  | Orally                  |
|                                  | Clopidogrel        | 75mg       | Daily                  | Orally                  |
| Recurrent urinary tract infections | Ceftriazone       | 1g         | Daily                  | Intramuscularly         |
|                                  | Saccharomyces boulardii | 250mg | Daily                  | Orally                  |
| Type 2 diabetes mellitus         | Insulin glargine   | 40units    | Nightly                | Subcutaneously          |
|                                  | Insulin lispro     | Sliding scale | Three times daily before meals | Subcutaneously          |
| Vitamin deficiencies            | Ascorbic acid      | 500mg      | Daily                  | Orally                  |
|                                  | Cholecalciferol    | 1000units  | Daily                  | Orally                  |

Abbreviations: PGx: Pharmacogenomics

Results of the PGx test (Table 2) were assessed against the patient’s medication regimen (Table 1), aided with an advanced CDSS [(MedWise® (Figure 1)]. The PGx results identified the patient as a CYP2D6 normal metabolizer (NM) suggesting that a normal response to oxycodone was expected based her genotype results (CYP2D6*1*2A). However, the pharmacist noted that there was a drug-drug-gene interaction (DDGI) with duloxetine, resulting in phenoconversion to a CYP2D6 intermediate metabolizer (IM) for oxycodone [5,13]. This DDGI could result in reduced formation of the more potent metabolite, oxymorphone, and could increase the risk of pharmacotherapy failure and may contribute to the patient’s inadequate pain management [5]. In addition, several drug-drug interactions (DDIs), particularly with oxycodone, were identified (Figure 1), including competitive inhibition at CYP3A4 due to the coadministration of amlodipine and atorvastatin [14,15]. When these two drugs are coadministered with the weaker affinity substrate oxycodone, concentrations of oxycodone would increase, thus increasing the risk for oxycodone-related ADEs (e.g., drowsiness, headaches) [16]. CYP2D6 DDGI, taken together, were deemed associated with suboptimal pain management while CYP3A4/5 DDI could explain daytime sedation.
Table 2: Patient’s PGx Results.

| Gene              | Result          | Phenotype                                              |
|-------------------|-----------------|--------------------------------------------------------|
| CYP1A2            | *1A/*1F         | Normal Metabolizer (Hyper-inducibility)†               |
| CYP2B6            | *1/*1           | Normal Metabolizer                                     |
| CYP2C9            | *1/*1           | Normal Metabolizer                                     |
| CYP2C19           | *1/*1           | Normal Metabolizer                                     |
| CYP2D6            | *1/*2A          | Normal Metabolizer                                     |
| CYP3A4             | *1/*1           | Undetermined                                           |
| CYP3A5            | *3/*3           | Non-Expresser                                          |
| SLCO1B1 (rs4149056) | *1A/*1B       | Normal Function                                        |
| HLA-A             | *31:01          | Positive                                               |
| HLA-B             | *15:02          | Negative                                               |

Abbreviations: CYP: Cytochrome P450, PGx: Pharmacogenomics, HLA: human leukocyte antigen; †Common variants in CYP1A2 gene reflect its inducibility. CYP1A2 genetic variations, without the presence of induction (e.g., smoking, concomitant CYP1A2 inducers), have not been demonstrated to clinically alter the activity of CYP1A2 [19]. ‡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 [20].

As the patient’s pain symptoms were related to TGN, alternative medications were evaluated considering the patient’s PGx results, renal function, and potential for drug-gene interactions (DGIs) and DDGIs (Table 3) [17,18,21]. As the patient was prescribed gabapentin 100mg three times a day for neuropathy, the clinical pharmacist recommended optimizing the morning dose to 200mg [17,18,22]. In addition, it was suggested to discontinue oxycodone/acetaminophen. Recommendations and awareness are described in Table 3.

Approximately 2 weeks after implementing these drug regimen modifications, the patient reported feeling significantly less sedated with better pain control (NRS = 0). The patient’s quality of life was improved so significantly that she began considering pursuing prosthetic implantation in hopes of walking again.

Discussion

The simultaneous management of pain and multiple comorbidities can present clinicians with challenges. As presented in this case, pain can lead to reduced physical activity, decreased energy level, and depression; and depression can lead to more pain. Furthermore, side effects associated with medicine used to control these conditions may lead to daytime sedation, worsening lethargy, energy, and physical activity. This describes the often-observed prescription cascade: a medication prescribed to treat one condition worsens another condition or causes a new one, leading to the introduction of another drug [23]. This patient case is an example of how incorporating PGx information with drug-induced phenoconversion can successfully improve PGx result interpretation in the presence of polypharmacy. This case report illustrates that integrating PGx can help determine appropriate pain management therapy, mitigate opioid use, identify oxycodone-related side effects, and improve patient quality of life.

In this case study, the patient’s pain was inadequately controlled despite being prescribed pain analgesic oxycodone/acetaminophen. Oxycodone is primarily metabolized by the CYP3A4 enzyme into an inactive metabolite, noroxycodone, while ~10% is metabolized by the CYP2D6 enzyme into a more potent metabolite, oxymorphone [24-26]. To exert their effects, both oxycodone and oxymorphone bind and activate mu-opioid receptors, located in several organs including the brain. Oxymorphone has up to 60 times stronger affinity than oxycodone [27]. Higher concentrations of oxycodone, a weak CYP3A4 affinity substrate, were predicted for this patient due to DDIs and competitive inhibition from the concomitant administration of the CYP3A4 moderate-affinity substrates, atorvastatin and amlodipine (Figure 1) [5,14,15]. The patient’s excessive sedation and headaches were likely worsened by increased oxycodone levels, negatively affecting her quality of life [16,28,29].
**Figure 1:** Summary of CYP450 affinity and metabolic pathways of patient’s drug regimen.

| Substance       | CYP1A2 | CYP2B6 | CYP2C19 | CYP2D6 | CYP3A4 |
|-----------------|--------|--------|---------|--------|--------|
| Acetaminophen   |        |        |         |        |        |
| Amlodipine      |        |        |         |        |        |
| Atorvastatin    |        |        |         |        |        |
| Clopidogrel†    |        |        |         |        |        |
| Duloxetine      |        |        |         |        |        |
| Melatonin       |        |        |         |        |        |
| Oxycodone       |        |        |         |        |        |
| Pantoprazole    |        |        |         |        |        |

Abbreviations: CYP: Cytochrome P450, PGx: Pharmacogenomics
†Only CYP-metabolized oral medications are displayed
‡Prodrug

MedWise® demonstrates substances with their differing metabolic pathways and their differing binding affinities (e.g., light yellow = weak affinity, dark yellow = moderate affinity).

Legend:

| Weak Substrate | Moderate Substrate |
|----------------|-------------------|

The utilization of PGx testing and CYP2D6 results to inform personalized treatment plans has proven to help overcome the inappropriate prescribing of opioids [7]. Although the Clinical Pharmacogenetics Implementation Consortium do not provide CYP2D6-specific therapeutic recommendations for oxycodone, substantial evidence supports the relationship between oxymorphone concentrations and analgesic effects [16,28,30]. A recent review highlighted the reasons for some conflicting results between CYP2D6 polymorphisms and oxycodone response [5]. Among those, the authors highlighted that 1) CYP2D6 is expressed in the liver and in the brain; 2) local formation of oxymorphone in the brain is possibly independent of liver activity; 3) genetically-determined poor metabolizers (PM) of CYP2D6 cannot form oxymorphone in the liver and brain; 4) CYP2D6 PMs do not exhibit pain control when administered oxycodone; 5) CYP2D6 inhibition (leading to phenoconversion) could be observed in the liver only or in the liver and in the brain, depending on the capability of the perpetrator drug to cross the blood brain barrier; 6) thus, under certain conditions, oxymorphone formation could be prevented in the liver leading to low circulating plasma levels while its formation could still occur in the brain [5].

In order for complete phenoconversion to occur (decreased oxycodone efficacy), perpetrating medications must also be able to cross the blood brain barrier [5,29]. Such condition is observed in the current case, as duloxetine, a CYP2D6 moderate-affinity substrate, must accumulate in the brain to exert its effects; therefore, when administered with the CYP2D6 weak-affinity substrate oxycodone, duloxetine can induce a phenoconversion in the brain of CYP2D6 NM to IM [5,13]. This DDGI results in a decreased transformation of the parent drug, oxycodone, into the more potent metabolite, oxymorphone, both in the liver (systemically) and in the brain (locally) [5,27,29].

To address the patient’s pain and the expected increased risk for oxycodone-related ADEs and pharmacotherapy failure, alternatives were considered and analyzed for the TGN symptoms. TGN is a rare, chronic pain condition due to nerve dysfunction of the trigeminal nerve [17]. Pharmacological treatment options for improving pain symptoms include several anticonvulsants, with carbamazepine or oxcarbazepine being first-line treatment [17,18,21]. Based on the patient’s PGx results (positive for the HLA-A *31:01 allele), the first-line options carbamazepine and oxcarbazepine were excluded due to the increased risk for severe life-threatening cutaneous reactions (e.g., Stevens Johnson syndrome) [31,32]. In addition, these medications possess sedative properties, and drug monitoring would have been necessary since DDIs and DDGIs were expected (Figure 2, Table 3) [33-35].
Figure 2: Summary of CYP450 affinity and metabolic pathways of the alternative medications considered for TGN therapy and the patient’s current medications that would be subsequently affected by DDIs†.

| Substance       | CYP2B6 | CYP2C9 | CYP2C19 | CYP3A4 |
|-----------------|--------|--------|---------|--------|
| Amlodipine      |        |        |         |        |
| Atorvastatin    |        |        |         |        |
| Clopidogrel‡    |        |        |         |        |
| Carbamazepine   |        |        |         |        |
| Oxcarbazepine   |        |        |         |        |
| Phenytoin       |        |        |         |        |
| Topiramate      |        |        |         |        |

Abbreviations: CYP: Cytochrome P450, DDI: Drug-drug Interactions, TGN: Trigeminal Neuralgia

†Only CYP-metabolized oral medications are displayed
‡Prodrug

MedWise® demonstrates substances with their differing metabolic pathways and their differing binding affinities (e.g., light yellow = weak affinity, dark yellow = moderate affinity).

Legend:

Other second-line TGN treatments were evaluated for appropriateness, including phenytoin and topiramate [17,18]. Given the patient’s CYP2C9 and HLA-B*15:02 results, no DGIs affecting phenytoin and topiramate were identified (Table 2) [36]. However, if either one of these medications were included in the medication regimen, they would cause several DDIs due to induction of CYP2B6 and CYP2C9 by phenytoin, and of CYP3A4 by phenytoin and topiramate (Figure 2, Table 3) [37,38]. Of the remaining medications evaluated, gabapentin does not utilize CYP enzymes for metabolism, thus would not contribute to CYP DDIs [22]. It was decided to optimize gabapentin instead of introducing another medication, as the current dose was sub-optimal for TGN and was below the 900mg daily maximum dose appropriate for the patient’s creatinine clearance of 45.9ml/min. [18,22].
Table 3: Clinical pharmacist’s patient-specific summary of potential therapies for TGN and comprehensive recommendations conveyed to the provider.

| Medication Reviewed | Rationale | Clinical Pharmacist Recommendations |
|---------------------|-----------|-------------------------------------|
| Oxycodone/acetaminophen 5mg/325mg | • Competitive inhibition at CYP3A4 (amlodipine and atorvastatin); increasing risk of toxicity.  
• PGx results CYP2D6 NM but phenoconversion to CYP2D6 IM for oxycodone due to duloxetine; increasing risk of pharmacotherapy failure.  
• Oxycodone is working, but patient is experiencing over sedation.  
• Additionally, oxycodone is not appropriate for trigeminal neuralgia treatment. | Consider discontinuing oxycodone. See below assessments for potential alternatives for TGN:  
Carbamazepine (1st line)  
• DGI: Patient is positive for \textit{HLA-A*31:01}, translating to a higher risk for severe hypersensitivity reactions. Suggested to avoid carbamazepine.  
• DDI: Carbamazepine induces CYP3A4 metabolism, which will result in decreased concentrations of amlodipine and atorvastatin and increased activation of clopidogrel.  
Oxcarbazepine (1st line)  
• DGI: This patient is positive for \textit{HLA-A*31:01} thus has a higher risk for hypersensitivity reactions with oxcarbazepine when compared to carbamazepine (weaker evidence).  
• DDI: Oxcarbazepine inhibits CYP2C19 metabolism, which will result in phenoconversion to a CYP2C19 PM for pantoprazole and clopidogrel. An alternative antiplatelet therapy will need to be considered if used.  
Phenytoin (2nd line)  
• DGI: Patient is negative for \textit{HLA-B*15:02} and is expected to have a typical risk for hypersensitivity reactions with phenytoin. Limited evidence available to suggest phenytoin cannot be used with those \textit{HLA-A*31:01} positive.  
• DDI: Phenytoin induces CYP2B6, CYP2C9, and CYP3A4 metabolism, which will result in decreased concentrations of amlodipine and atorvastatin (monitoring closely for effectiveness will be recommended) and increased activation of clopidogrel.  
Topiramate (2nd line)  
• No DGIs  
• DDI: Induces CYP3A4 metabolism, which will result in decreased concentrations of amlodipine and atorvastatin (monitoring closely for effectiveness will be recommended) and increased activation of clopidogrel.  
Baclofen and lamotrigine (2nd line)  
• DGI: Limited evidence available to suggest lamotrigine cannot be used with those \textit{HLA-A*31:01} positive.  
• No DGIs with baclofen.  
• No DDI via CYP enzymes for either medication.  
Gabapentin (2nd line)  
• No DGIs  
• No DDIs via CYP enzymes  
• Currently prescribed for neuropathy at 100mg three times a day with room to optimize given patient’s creatinine clearance of 45.9ml/min. |
A de-prescribing strategy was considered to mitigate oversleepiness due to CYP1A2 DDI, as duloxetine can cause sleepiness and act as a competitive inhibitor of melatonin metabolism, a weak CYP1A2 affinity substrate (Figure 1, Table 3) [39]. Ultimately, the provider increased the morning dose of gabapentin to 200mg (400mg daily) and discontinued melatonin and oxycodone/acetaminophen; close monitoring was continued for pantoprazole and clopidogrel.

After adjusting the patient’s medication regimen, her pain was controlled (NRS = 0) and her quality of life significantly improved, which initiated her pursuit to walk again. Lemke et al. reported that incorporating and discussing PGx findings offers reassurance and psychological benefit to the patients [40]. Given that some patients are cautious and sometimes hesitant to discontinue or change their medication, particularly opioids, presenting them with PGx-driven personalized assessments can help earn the patients’ trust.

**Conclusions**

Employing a personalized, multimodal approach to pain management demonstrates promise in implementing changes regarding the overuse and misuse of opioids. This case demonstrates that in the context of polypharmacy, integration of pharmacogenomic information into a decision-making process is successful when concomitant medications are considered. This resulted in improvement in medication safety, in the patient-provider relationship, and in the patient’s overall quality of life as she strives to walk again.

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