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COMMENTARY

Genetic Testing for Opioid Pain Management: A Primer

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ABSTRACT

Patients see their primary care physicians (PCPs) for a variety of medical conditions, chronic pain being one of the most common. An increased use of prescription medications (especially opioids) has led to an increase in adverse drug reactions and has heightened our awareness of the variability in response to medications. Opioids and other pain adjuvants are widely used, and drug–drug interactions involving these analgesics can be problematic and potentially lethal. Pharmacogenetics has improved our understanding of drug efficacy and response, opened doors to individual tailoring of medical management, and created a series of ethical and economic considerations. Since it is a relatively new field, genetic testing has not been fully integrated into the primary care setting. The purpose of this paper is to review the metabolism of commonly prescribed opioids, discuss the economic and ethical issues, and provide PCPs with an understanding of how to incorporate genetic testing into routine use to improve clinical practice and patient management.

Keywords: Adverse drug reactions; Chronic pain; Drug interactions; Opiates; Opioids; Opioid metabolism; Pharmacogenetic testing

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INTRODUCTION

Chronic pain is one of the most common reasons that patients visit physicians in the primary care setting [1]. With a rapidly aging population, primary care physicians (PCPs) are seeing a higher incidence of chronic pain conditions. These patients are often plagued with multiple medical problems, which make their medication management more challenging. Pain medications are some of the most commonly prescribed drugs in the United States, with opioids continuing to be the mainstay of chronic pain management [2, 3]. Adjuvant therapies such as antidepressants, benzodiazepines, anti-inflammatory agents, or anticonvulsants can also be useful in managing pain, and many (if not most) pain patients may be treated with a combination of these medications. Therefore, PCPs must be increasingly

aware of the potential risk for drug-to-drug interactions. Fatal adverse drug reactions have been reported to be the fourth leading cause of death in the USA [4]. In addition, the "trial-and-error" approach to prescribing medicine is costly and causes delays in effective care. As personalized medicine becomes more prevalent, these costly approaches to medical care will eventually become obsolete, and streamlined methods guiding therapeutic decisions will prevail.

One of the tools available for implementing a more personalized approach, with greater optimization of patient outcomes, is pharmacogenetic testing. Pharmacogenetics is a type of genetic test that assesses a patient's risk of an adverse response or likelihood of responding to a given drug, thereby informing drug selection and dosing [5]. As the personalized medicine movement gains momentum, pharmacogenetic testing will be important across all medical specialties, with an emphasis in primary care, since a majority of all prescription drugs are written in this setting [6].

Pharmacogenetics is a relatively new field, and as yet it is only slowly being integrated into the primary care setting. Many PCPs are still not familiar with how to test, interpret, or apply this technology in clinical practice [7]. This paper serves as a primer for PCPs to enhance their understanding of pharmacogenetics, with a focus on opioid pain medications.

The article is based on previously conducted studies, and does not involve any studies of human or animal subjects performed by any of the authors.

OPIOID METABOLISM

To understand how opiates are metabolized, it is necessary to start with related terminology. Pharmacokinetics is the process by which the body absorbs, distributes, metabolizes, and excretes drugs, while pharmacodynamics describes the drug's effects on the body at the cellular or receptor level [8].

Genetic polymorphism is the term for variations in the structure of genes, which includes structural changes such as deletion, duplication, and translocation. Each of these gene alterations is called an allele of the original gene (wild-type). Having two copies of the same allele is called a homozygous genotype, while having any combination of two different alleles is called a heterozygous genotype. A single-nucleotide polymorphism (SNP) is the most common altered gene form.

Patients can be classified by their genetic ability to metabolize a medication: a normal metabolizer (NM) responds as expected when given a medication and has two normal or "wild-type" alleles; an intermediate metabolizer (IM) can have partially active alleles or one fully defective allele; a poor metabolizer (PM) has two abnormal alleles with minimal gene activity; a rapid metabolizer (RM) has at least one highly active allele, and an ultra-rapid metabolizer (UM) can have many copies of the normal gene, leading to activity many times the baseline level [9].

These changes in alleles may have a significant effect on pain perception and opioid use. A retrospective chart review analyzed the DNA of female postoperative patients and concluded that smokers and those possessing the PM genotype were more likely to experience severe postoperative pain than other patients (71% vs. 26–28% in all the other groups combined), based on self-reported pain scores and opioid intake [10].

With the exception of morphine, oxymorphone, and hydromorphone, opioid metabolism is primarily mediated by the cytochrome P450 enzyme system located in the liver [11]. This enzyme system is extensively involved in the metabolism of drugs as well as other chemicals, foods, or toxins in the body. Although more than 30 CYP450 isoenzymes have been identified, seven of these are clinically important: CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4, whose presence and activity levels vary based on a variety of factors including race, ethnic background and tobacco abuse [9] as well as interactions with other medication, and other receptors, such as the opioid receptors [12].

Clinicians have always noted a wide variability in patient response to opioid pain medications. In the past, this has been attributed to differences in gender, body mass, or cultural factors influencing pain perception [13, 14].

However, genetics appears to play a larger role in the clinical efficacy of opioid medications than was previously thought, which is related to the high inter-individual variability in the activity level of the CYP system [15, 16]. Further discussion in this article will be limited to the isoenzymes with a significant impact on pain medication metabolism [9, 17].

CYP2D6

CYP2D6 is responsible for the metabolism of most of the commonly prescribed opiate medications, including codeine, tramadol, hydrocodone, and oxycodone. Decreases in CYP2D6 activity may lead to reduced conversion of prodrugs into their more active metabolites, causing inadequate analgesia and the need for increased opioid medication. Conversely, increased CYP2D6 activity can lead to elevated levels of active metabolites in the blood, increasing the risk of adverse outcomes (such as an overdose) [18]. At present, over 80 subtypes of the CYP2D6 allele have been identified, and their prevalence varies by race and ethnicity [9, 18]. Almost 10% of the white population lacks a good copy of this gene [19].

CYP2D6 metabolizes inactive codeine to its active form. morphine; inactive hydrocodone is metabolized into the active hydromorphone; active oxycodone is metabolized into the more active oxymorphone; and less active tramadol is metabolized into the more active *o*-desmethyltramadol [8]. A common clinical scenario is as follows: Codeine (a prodrug) is given to a patient who is a PM for the CYP2D6 gene. Because of this genetic makeup, the patient is unable to convert enough of the prodrug into its active form to obtain relief, and may be accused of drug-seeking if they complain of inadequate analgesia. If the patient is an RM or UM, they can experience a higher than expected level of sedation, addiction, and other systemic side effects at lower doses than standard metabolizers [18]. In a 2007 study, the area-under-the-curve (AUC) diagram of morphine concentration over time varied at least 30-fold between PM and UM patients taking codeine [18].

Tramadol is a weak mu opioid receptor agonist; however, CYP2D6 metabolizes the M1 metabolite (*o*-desmethyltramadol), which is many times more potent than the parent compound [20] and may cause adverse side effects in UMs [21]. Hydrocodone is a semi-synthetic codeine derivative, which is metabolized by CYP2D6 into hydromorphone, its active metabolite [19, 22]. Depending on patient classification (PM, UM, RM, etc.) and ratio of parent compound to active metabolite (as measured in urine), a large degree of variability in the clinical efficacy of this medication can be observed [9, 23].

Alternately, CYP2D6 may increase the fraction of inactive drug that is present. For example, oxycodone is active at the mu receptor [9]. Oxycodone is metabolized by CYP3A4 into noroxycodone, which has less than 1% of the activity of the parent compound. However, CYP2D6 subsequently converts that noroxycodone to noroxymorphone and then converts oxycodone to oxymorphone (dual metabolism); therefore, PM patients may note improved analgesia while using this medication [9], and UM or RM patients may paradoxically note reduced analgesic efficacy [15].

Forty-five women who had undergone C-sections were treated postoperatively with codeine, and their genetic CYP2D6 status was evaluated. The two PM patients noted no analgesia, and two of the three UMs noted immediate pain relief from the codeine, but they stopped the medication due to dizziness and constipation [24]. The authors noted that the response to codeine matched their genetic status.

CYP3A4 and CYP2B6

The CYP3A4 system regulates the excretion of fentanyl, methadone, and buprenorphine. PM patients or those who are taking oral CYP3A4 inhibitors (e.g. grapefruit juice, verapamil, diltiazem, clarithromycin) [25] have a higher risk of elevated blood levels and subsequent toxicity [9].

Methadone is a synthetic opioid with *n*-methyl-D-aspartate (NMDA) inhibitor, serotonin reuptake, and norepinephrine reuptake

inhibitor properties [22]. It exists as R- and S--enantiomers, but most of its mu opioid activity is due to the R-enantiomer [22]. In the past, methadone was believed to be metabolized primarily by the CYP3A4 system [26], but more recent studies suggest that its major metabolism may instead be via CYP2B6 [27]. Interestingly, polymorphisms in the CYP 2B6 gene have been associated with differences in methadone treatment dose requirements in individuals managed for opioid addiction [28]. Polymorphisms at the CYP2B6 enzyme may also account for the variability in bupropion metabolism, [29, 30] and may be an important factor in the effectiveness of the reverse transcriptase inhibitor efavirenz [31], as well as ritonavir and nelfinavir [32].

CYP1A2

CYP1A2 partially biotransforms antipsychotic medications, such as clozapine and olanzapine [28], to their inactive form, so patients who are PM for the CYP1A2 appear to be at increased risk for toxic blood levels and increased incidence of tardive dyskinesia [33]. This is also the enzyme that metabolizes caffeine [34]. Both tobacco and marijuana smoking induce CYP1A2 activity, and their combined use is additive [35]. Therefore, when patients stop smoking, the increased metabolism of caffeine will decrease, leading to increased caffeine levels and therefore potentially increased agitation (which might be attributed to the smoking withdrawal) [36].

CYP2C9

CYP2C9 metabolism primarily involves NSAIDs and aspirin, though it is also the system that metabolizes phenytoin and warfarin. A recent study noted that the genetic screening of patients for defective variants of UGT1A6 (see below) and CYP2C9 helped identify those patients at risk for gastritis from aspirin use [37]. Up to 31 defective variants of the CYP2C9 have been found to cause reduced clearance of diclofenac [38], potentially increasing the risk of GI and renal adverse events. Poor metabolizers make up about 8–12% of white populations [39, 40], but it is rare in Ethiopian (4%) and extremely rare in African-American (1%) and Asian populations [40] (0% of Koreans in one study) [41].

CYP2C19

CYP2C19 primarily affects the metabolism of diazepam and carisoprodol, as well as clopidogrel, proton pump inhibitors, and several antidepressants. CYP219 metabolizes amitriptyline, clomipramine, doxepin, imipramine, and trimipramine, and PMs of CYP2C19 need about 60% of the standard dose of these medications, while UMs need about 110% of the standard dose [29]. Cannabinoids are probably significant CYP2C19 inhibitors [34] (which may raise diazepam blood levels). Proton pump inhibitors such as omeprazole and esomeprazole are also CYP2C19 inhibitors [42]. There are at least 27 variant alleles that have been identified [43]. Poor metabolizers of CYP2C19 are seen more commonly in Asian, Swedish, and Ethiopian populations (12–23%) compared to whites (2–5%), while 18% of Swedes and Ethiopians and 4% of Chinese are UMs of CYP2C19 [43].

UDP-Glucuronosyltransferase

One of the most common non-CYP enzymes associated with pain medications is UDP-glucuronosyltransferase (UGT) [44]. UGT is the main metabolizer of morphine, creating morphine-6-glucuronide (M3G), which contributes to pain relief, and morphine-3-glucuronide (M3G), which is hyperalgesic (causing increased pain). An increased concentration of M3G is believed to contribute to the phenomenon of opioid hyperalgesia.

Other Receptors and Enzymes Associated with Opioids and Analgesics

Polymorphisms in the mu opioid receptor itself may cause reduced potency of opioid medications. For example, the mu receptor subtype OPRM1 is the primary site of action of most

opioid medications as well as endogenous endorphins. This receptor also controls the rewarding effects of nicotine and alcohol [45]. Whether the patient possesses the wild-type (two normal copies), heterozygous (one normal, one altered) or homozygous (two altered copies) alleles of this gene has been shown to influence postoperative opioid requirement after abdominal surgery [9]. One of the best-studied OPRM1 SNPs is 118A/G, with the G variant seen in 10–48% of tested patients, depending on the study [12]. Reynolds et al. found that patients carrying the GG genotype required much higher opioid doses to achieve pain relief [12].

Other receptors such as catechol-*o*-methyl transferase (COMT) have known variants (i.e. Val/Val, Met/Met) that are associated with increased opioid requirements, fibromyalgia, and a higher risk of addictive behaviors such as gambling and drinking [46]. In a study evaluating the role of genetics in predicting how well morphine would control cancer pain, Reyes--Gibby et al. found that the morphine dose needed by carriers of the OPRM1 GG genotype was 93% higher than that for carriers of the AA allele, and the lowest dose requirement was observed among carriers of the OPRM1 AA and COMT Met/Met genotype [13].

The P-glycoprotein 1 (permeability glycoprotein, abbreviated as P-gp or Pgp), also known as multidrug-resistant protein 1 (MDR1), is a glycoprotein that in humans is encoded by the *ABCB1* gene. The ABCB1/MDR1 transporter gene is a major determinant of morphine bioavailability, and, as stated above, the OPRM1 gene encodes for the mu opioid receptor, the primary site of morphine activity. Mutations in either of these two genes can affect the efficacy of morphine [47]. Campa et al. genotyped 145 patients for the SNP C3435T of the ABCB1/MDR1 gene and the A80G SNP of the OPRM1 gene (a different SNP than the A118G discussed above) and observed statistically significant variability in pain relief ($P < 0.00001$), allowing for the detection of three groups of patients—strong responders, intermediate responders, and non-responders—with close to 100% sensitivity and 70% specificity [48].

Drug–Gene Interactions

Many of the common medicines used in pain management are metabolized by the CYP450 system, i.e. they are substrates of this system (see Table 1). Some of the adjuvant medications used to treat pain, such as antidepressants, can significantly inhibit the activity of the CYP450 system, and therefore influence the effect of other medications such as opioids. For example, paroxetine [49] and duloxetine [50] are CYP2D6 inhibitors (but not citalopram or escitalopram), and would be expected to reduce the analgesia of opioids requiring CYP2D6 activity for activation (see Table 2). This can convert a genetically normal CYP2D6 metabolizer into a phenotypically poor CYP2D6 metabolizer.

Other medications can induce these CYP450 enzymes, increasing the effect of prodrug medications, causing patients to phenotypically become ultrametabolizers (see Table 3).

Thus there are several types of interactions between medications and genes: drug–drug interactions (DDIs), drug–gene interactions (DGIs), and drug–drug–gene interactions (DDGIs). Verbeurgt et al. looked at a sample of 1143 patients, genotyped them for CYP2C9,

Table 1 Common substrates of CYP enzymes

1A2	2B6	2C9	2C19	2D6	3A4
Acetaminophen	Bupropion	Celecoxib	Diazepam	Codeine	Alprazolam
Melatonin	Methadone	Piroxicam	Carisoprodol	Tramadol	Midazolam
Caffeine		Ibuprofen		Oxycodone	Methadone
		Warfarin		Hydrocodone	Fentanyl
					Buprenorphine

Table 2 Common inducers of CYP enzymes

1A2	2B6	2C9	2C19	2D6	3A4
Tobacco	Phenobarbital	St. Johns Wort	Rifampin	Rifampin	Phenobarbital
Cannabinoid		Rifampin	Gingko	Dexamethasone	Rifampin
Oxcarbazepine		Ritonavir	Prednisone		Butalbital
Carbamazepine					
Phenobarbital					

Table 3 Common inhibitors of CYP enzymes

1A2	2B6	2C9	2C19	2D6	3A4
Ciprofloxacin	Paroxetine	Fluoxetine	Fluoxetine	Duloxetine	Clarithromycin
Caffeine	Venlafaxine	Fluconazole		Paroxetine	Erythromycin
Grapefruit				Fluoxetine	Grapefruit
				Goldenseal	Indinavir
				Bupropion	Ritonavir

CYP2C19, and CYP2D6, and then looked at drug–gene and drug–drug–gene interactions [51]. The total number of medications that these patients were prescribed ranged from 1 to 44, with a mean of 8.4 and a median of 7 medications. The authors found that 31% of the patients had a DDI, 12% had a DGI, and 12% had a DDGI.

THE INS AND OUTS OF GENETIC TESTING

Why Test Patients?

Effective pain management can be challenging, especially in settings where potent analgesics are used to treat patients with a high level of pain, and the patients do not respond to therapy or experience side effects. In addition, comorbidities requiring polypharmacy complicate decisions regarding which medications can be prescribed [51]. Genetic testing may be most useful in these types of settings and may provide data to determine the most efficacious drugs to prescribe at the safest dosing. Other scenarios in which genetic testing may be useful include patients who have shown a poor response to medications in the past, those with a family history of drug sensitivity, and selected pediatric patients [52] or breastfeeding mothers [53] prior to starting codeine.

Ethical Considerations of Testing

Even as genetic testing is becoming more widely accepted, many ethical questions have yet to be fully addressed. At the forefront is the concern that pharmacogenetics may exacerbate inequalities in the delivery of healthcare. Thus far, most debate surrounding genetic testing has been linked to genetic disorders and the potential impacts that knowledge of this information could have [54]. The use of pharmacogenetic tests to examine variation in treatment response raises a different set of ethical issues from other forms of genetic testing [54]. Expanding the use of genetic information could have consequences for both patients and their family members. Emerging research on genetic testing of opioid receptors may make it possible to identify those at high risk of opioid abuse and addiction [9]. Information obtained from

pharmacogenetic testing could help to predict a patient's susceptibility to certain diseases or the response of family members to particular drugs [55].

This leads to several ethical questions. Should health insurance companies or employers have access to this information? Will pharmacogenetic testing be mandatory in the future? With the availability of this information, would individuals be subject to higher health insurance premiums because they have the potential for a "poor response" to certain treatments? Moreover, where should the responsibility lie for obtaining pharmacogenetic testing? Should the tests be available for individuals to purchase online, over the counter? Or should they be available only through a PCP who is making a decision about prescribing a particular medication? If this information does guide a PCP's decision, then what if that patient's insurance disallows particular therapies?

Pharmacogenetic information can vary according to racial or ethnic origin. For instance, as described above, variations in the gene for the enzyme CYP2D6 are known to differ among racial groups [56]. What might be the implications of finding a genetic variant that influences a medicine's response in a particular ethnic group? Among Ethiopian and Saudi Arabian populations, researchers found a high frequency of a genetic variant associated with increased CYP2D6 activity. In contrast, 7–10% of a white population possessed a genetic variant resulting in reduced activity of this enzyme [57].

Information like this has the potential to lead to the design of medications for a specific ethnic group or for an ethnic group most likely to be able to afford the medications [54]. As noted by Lipton [54], "There could be implications both for the conduct and design of research, and for the provision of tests and medicines. Will pharmacogenetics increase the likelihood of grouping of patients according to racial or ethnic groups for medical purposes? If so, what might be the ethical and social implications of such an outcome?"

These and other ethical questions will continue to arise as utilization of genetic testing becomes more sophisticated and thus more mainstream. Will the knowledge (or perceived knowledge) of genetic status change the way that patients are treated? A study of 134 chronic non-cancer pain patients found that physicians adjusted treatment plans for close to half of patients genotyped for pain perception-related COMT, and they perceived the genetic test results as consistent with patient pain levels in 85% of cases [58]. As such, these genetic tests carry significant weight. It is very concerning, therefore, to read case reports such as that by Zittel et al., who described a nurse who forged her genetic report to "confirm" her "dopa-responsive dystonia", supporting her apparent Munchausen symptoms [59].

Many of these issues with regard to pharmacogenetics will have to be carefully addressed before the benefits and clinical applications of pharmacogenetics can be fully integrated into modern medicine. This will require healthcare professionals and policymakers to work together to continuously address issues regarding patient confidentiality, access to information, affordability, and research ethics in order to avoid such disparities.

Economic Considerations of Testing

Advances in pharmacogenetics have made the idea of "personalized medicine" more obtainable and provide a potential avenue for optimizing patient outcomes while reducing healthcare costs [60]. In cancer treatment, the use of genetic testing has become indispensable, improving outcomes, reducing side effects, and avoiding unnecessary testing [61]. In a review of the literature, 70% of 71 cardiac drugs studied had positive evidence of a varied response or adverse effect based on genetics. The authors stated that "considerable clinically actionable pharmacogenomic information for cardiovascular drugs exists, supporting the idea that consideration of such information when prescribing is warranted" [62]. However, the use of genetics in pain medicine has lagged these other fields.

While pharmacogenetic tests are becoming more affordable, access is still limited, and the costs that are related to obtaining samples, as well as interpreting and counseling patients on

results, still need to be accounted for. In a broader sense, as our testing becomes more precise and our data accumulate, the promise that these results could reduce the trial-and-error approach to medication prescribing and reduce the likelihood of hospitalizations due to adverse drug reactions could significantly impact the economics of healthcare [63].

Researchers at Harding University recently conducted a randomized controlled trial in a high-risk population of chronically ill polypharmacy patients aged 50 years and older who were admitted to home health care after an inpatient hospitalization. The trial was designed to add pharmacogenetic data in an integrated clinical information system compared to a standard drug information system. The data showed that readmissions were reduced by 52% ($P = 0.007$), emergency department (ED) visits by 42% ($P = 0.045$), and mortality by 85% ($P = 0.05$). The authors estimated a potential cost savings per patient of $4382 in just 60 days, based on Medicare average all-cause readmission and ED visit costs [64].

Greater precision in prescribing drugs could potentially streamline the costs associated with polypharmacy. In addition, the costs of developing new agents could be dramatically reduced with the use of pharmacogenetics, to about 60% of the $880 million on average currently spent in developing a drug [65].

As clinical utility and cost-effectiveness are still being debated, economics continues to be an important rate-limiting step in considering treatments and therapies, and will no doubt be a major factor in how pharmacogenetic testing is integrated into our current medical practice [66]. Furthermore, knowledge of which pharmacogenetic testing applications are appropriate in pain management may be used to tailor treatments and limit unnecessary costs as opposed to recommending global testing approaches [62].

The Ins and Outs of Testing

In current practice, when laboratory monitoring of patients taking pain medications is performed, it is largely through urine drug measurements. Most urine drug screens (UDS), especially physician office "point-of-service" (POS) dipsticks, will provide a positive versus negative result, but are fraught with false-positive and false-negative errors [67]. Quantitative urine drug toxicology (UDT) reports provide information on opioid metabolites, which can offer clues as to the genetic make-up of the patient [9].

Oral (saliva) drug sampling is becoming more prevalent and economically feasible [68]. The advantages of oral sampling include a low risk of tampering (since samples are taken under direct observation), its non-invasive nature, and easy sample collection. Drawbacks to oral collection are the shorter time that metabolized drugs remain in oral fluids compared to urine, and the lower efficiency in detecting certain drug use (e.g. marijuana).

The ratio of metabolites to the parent compound seen in the UDT can provide clues as to the genetic makeup of the patient. For instance, a patient taking hydrocodone who has very little hydromorphone in the urine might be genetically deficient in CYP2D6. However, this result might also be seen with a patient with normal CYP2D6 function who is also taking a CYP2D6 inhibitor. The combination of UDT and genetic testing can provide important insight into the phenotypical response of the patient to a medication.

Available Genetic Testing

Genetic testing is commonly performed with blood and saliva; however, even small amounts of cheek tissue from a buccal swab can now be used for genetic testing [69], with results showing accuracy comparable to that with serum samples [70]. Genetic testing can confirm the findings of the urine toxicology (poor CYP2D6 function in the above example), or it may show normal function, implying drug–drug interactions.

There are a variety of genetic panels available. Some look at only a few enzymes, typically CYP2C9, CYP2C19, CYP2D6, and VKOR1 (which is associated with warfarin levels). Other

panels may include OPRM1, COMT, and ABCB1, as well as dopamine receptors and transporters, serotonin receptors and transporters, and a growing list of other alleles.

You've Tested; Now What?

As the use of polypharmacy increases, it is important to be able to appropriately utilize genetic testing in clinical practice. The following case will help illustrate how to properly interpret results and avoid prescribing medications that may be harmful or ineffective.

A former police officer with multiple work-related neck and low back injuries and surgeries presented as a new patient from another pain clinic. He was taking oxycodone controlled-release 80 mg four times daily, with morphine immediate-release 15 mg every 8–12 h for breakthrough pain, but still complained of pain scores of 8–9/10 with no evidence of sedation. At this time, the differential diagnosis included opioid hyperalgesia (increased pain due to the opioids themselves), diversion or drug-seeking, poor absorption, or poor drug conversion. POS urine testing (qualitative) was positive for opioids and oxycodone. UDT (quantitative) showed the following: oxycodone >6400, noroxycodone >6400, oxymorphone 145, and hydromorphone 57.

The high levels of oxycodone and morphine should have first triggered concerns that the pills had been scraped into the collecting cup, but the noroxycodone proved that the drug had been absorbed and metabolized by the liver. It is not uncommon to find small amounts hydromorphone in the urine of patients on high doses of morphine, though it should be <1% of the morphine dose. Most striking is the extremely small amount of the active metabolite oxymorphone. Thus the problem was not poor absorption or drug-seeking; it still could have been opioid hyperalgesia, but the most likely diagnosis was low CYP2D6 activity. However, the patient was also on fluoxetine, a very potent CYP2D6 inhibitor, so the question remained: was he genetically a PM or a normal metabolizer taking a potent inhibitor? If the fluoxetine was the culprit, changing antidepressants might help, but if he was a PM, it would be necessary to change the opioid.

Genetic testing confirmed poor CYP2D6 status, and the patient was transitioned to an extended-release and immediate-release hydromorphone, with good relief, since hydromorphone does not require CYP2D6 metabolism.

In this case, urine toxicology coupled with genetic testing provided both the diagnosis and appropriate treatment options.

CONCLUSION

Chronic pain is one of the most prevalent medical conditions, and pain medications are some of the most commonly prescribed drugs in the United States today. Unfortunately, there is wide variability in patient response to pain and to pain medications, which may be related to pain origin, pain sensitivity, cultural differences, weight, age, and prior use of opiates, as well as genetic polymorphisms. The risks of long-term opioid use include death from overdose and drug interactions; the use of more objective measures (e.g. urine levels, genetic testing) rather than subjective measures (pain scores) should aid in determining efficacy, identifying diversion, ensuring patient compliance with therapy, and guiding the management of complex patients.

Over time, genetic testing has become more accessible and less expensive. However, there are very serious and complex ethical and financial concerns regarding its use that must be addressed prior to widespread implementation of this tool. And, while the current data are intriguing, there is still no clear evidence that genetic testing—at least for the general population—is effective. It may be appropriate for certain patient populations (such as those with significant family history of adverse drug reactions, pediatric patients, and chronic opioid users) and for specific clinical situations (such as a family history of genetic polymorphisms, inadequate analgesia on a significant amount of pain medications, or aberrant UDS results). These tests may therefore offer unique information in the primary care setting that could

aid in medical decision-making for the complex patient.

As noted by Reynolds et al. [12], with the knowledge of a patient's potential for positive response to a given pain medicine, a physician is armed with critical information that can guide therapeutic decisions in real time. The incorporation of pharmacogenetic biomarkers holds promise as a means of assessing a patient's risk of adverse events or likelihood of drug efficacy. Incorporation of such biomarkers is emerging at the forefront of personalized medicine, and has the potential to improve the utility and efficacy of current strategies and to guide the development of new approaches to pain management.

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