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REPORT

Exploring Rates of Abnormal Pharmacogenetic Findings in a Pain Practice

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ABSTRACT

Pharmacogenetic testing (PGT) is part of increasing efforts to personalize medicine, hopefully leading to better medication selection with more effective, less toxic therapies. Pharmacogenetic testing has relevance for chronic pain treatment, given the frequent comorbidities and polypharmacy. This retrospective study explored the prevalence of polymorphisms in a specialty pain practice in Louisiana. Pharmacogenetic testing was conducted for the cytochrome P450 (CYP) enzymes CYP2B6, CYP2C19, and CYP2D6, or the uridine diphosphate-glucuronosyltransferase 2 family polypeptide B15 (UGT2B15) enzyme utilizing a noninvasive, saliva-based test based on clinical decision-making. The sample consisted of 61 men (58.7%) and 41 women (39.4%), with an average age of 46.7 years (range = 23–83, SD = 11.5 years). Across all tests, 164 (42.3%) were extensive, 99 (25.5%) were intermediate, 28 (7.2%) were ultrarapid, and 27 (7%) were poor metabolizers. Only three patients who had been tested were found to be extensive (normal) for all four genes. These data demonstrate that genetic polymorphisms were frequently encountered. Consideration should be given to obtaining PGT as an aspect of evaluation and treatment planning when working with patients in need of specialty pain consultation and care. Caution is needed, as this brief report encompasses results from a single pain practice in one geographic location with a potentially distinct prevalence of genetic polymorphisms. Further prospective study is needed.

KEYWORDS opioids, pain, pharmacogenetics, polymorphism, prevalence

INTRODUCTION

Pharmacogenetic testing (PGT) is a relatively new tool that promises to help improve outcomes in many areas of medicine, including pain management. Pharmacogenetic test results can assist clinicians in choosing medications that are more likely to benefit an individual patient while minimizing risks, thus contributing to the goal of "personalized medicine." The use of PGT can also be a valuable tool in "troubleshooting" when patients are having idiosyncratic reaction, require higher than normal doses, or simply exhibit poor response to a specific medication or a class of medications.

Pharmacogenetic testing has many potential uses, offering insight and guidance on the management of complex patients, many of whom have struggled with particularly problematic side effects or suboptimal benefits from medication regimens such as opioids.[1,2] In pain management specifically, PGT can guide personalized treatment plans, identify medication metabolism abnormalities, clarify and validate urine drug testing (UDT) results, help clinicians avoid potential medication interactions, and guide therapeutic decision-making such as dose adjustments, changes in medication dose, or opioid rotation.[3–8] This information, combined with general risk assessment strategies, a thorough history and physical examination, knowledge of potential concomitant medication interactions, and urine drug

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testing, can improve understanding of the unique and highly individualized responses to treatment so often seen in specialty care settings.[9,10]

Passik and Weinreb described the 4As (Analgesia, Adverse effects, Aberrant drug-related behaviors, and Activities of daily living) as the four key domains of outcome in pain management.[11] Pharmacogenetic testing can help explain unexpected outcomes in each domain. Poor analgesia, for example, may be the result of abnormal metabolism of a particular pain medication or of a medication interaction potentially impacting the outcome. Likewise, adverse effects can sometimes be explained by PGT for similar reasons. Suspected and ambiguous aberrant behavior including unexpected findings on urine drug testing can sometimes be better understood on the basis of PGT results (see below). Finally, activity level can be diminished in people with poor pain control, increased levels of side effects, or both. Performing PGT, when outcomes in these domains are less than hoped for, can directly lead to changes in medications and other management strategies that may help the patient and offer scientific justification for ongoing opioid therapy.

A large pain practice in Louisiana recently chose to obtain PGT on all new patients seen at their facility. One of the authors (E.E.) was the physician at this facility. This physician had been struggling with a number of patients with difficult and idiosyncratic reactions to commonly used medications and was also trying to manage the polypharmacy that is all too common in the management of refractory pain by the time patients ultimately end up in specialty pain care. The physician surmised that patients referred to a pain specialist's care might potentially have a higher incidence of abnormal PGT based on the fact that they did not respond to the more typical interventions offered in primary care.

Although there is currently no guideline establishing a standard of care for the decision to utilize PGT, the decision to test all new patients was based upon this physician's clinical observations of multiple factors, including poor analgesic response to many commonly used opioids, failures of multiple opioid trials, and/or poor tolerance to these commonly used medications. Cases were also observed suggestive of aberrant behaviors that may have been, in some patients, responses to the poor analgesia on the part of patients (for example, use of "borrowed" nonprescribed opioids from friends and family when the patient's own medications were ineffective). Finally, some other unexpected UDT findings, such as parent drug present in the urine though the sample was missing the major metabolite, had been a clinical finding observed amongst patients in the clinic prior to embarking on clinic-wide PGT. This had occurred in patients whom, in the physician's assessment, were unlikely to have been "shaving" tablets into their specimens.

This study reports on the results of 104 consecutive patient samples submitted to a laboratory for PGT on three subtypes of the cytochrome P450 (CYP) enzyme system (CYP2B6, CYP2C19, and CYP2D6), a superfamily of monooxygenases that catalyze the oxidation of substances such as medications in phase I or liver metabolism, and one test on the uridine diphosphate-glucuronosyltransferase 2 family polypeptide B15 (UGT2B15) enzyme, which plays a role in phase II metabolism in the kidneys or glucoronidation. These markers impact metabolism of a variety of medications, and a partial listing of the drugs impacted by these pathways are listed in Table 1.[12] As specific examples, CYP2B6 of the larger CYP450 system has clinical interest for the use of methadone, CYP2C19 has implications for the use of many antidepressants, and CYP2D6 has implications for opioids such as hydrocodone and oxycodone among others, and the phase II glucoronidation impact from UGT2B15 has implications for several benzodiazpeines (see Table 1). Although not all genetic polymorphisms will necessarily have a negative impact on health, and indeed may be harmless in many cases, the specific four markers chosen for study here do have the potential to impact both the clinical safety

TABLE 1. Partial List of Drugs Metabolized by Specific Enzyme

Cytochrome P450, phase I enzymes			Glucuronidation, phase II enzyme
CYP2B6	CYP2C19	CYP2D6	UGT2B15
Bupropion	Amitriptyline	Atenolol	Diazepam
Cyclophosphamide	Carisoprodol	Amitriptyline	Lorazepam
Efavirenz	Citalopram	Aripirazole	Oxazepam
Ifosphamide	Clomipramine	Atomoxetine	Temazepam
Methadone	Clopidogrel	Carvedilol	
Sorafenib	Cyclophosphamide	Clomipramine	
	Diazepam	Codeine	
	Escitalopram	Desipramine	
	Indomethacin	Duloxetine	
	Lansoprazole	Fluoxetine	
	Nelfinavir	Haloperidol	
	Pantoprazole	Hydrocodone	
	Phenobarbital	Imipramine	
	Primidone	Lidocaine	
	Progesterone	Mexilitene	
	Propranolol	Nortriptyline	
	Sertraline	Oxycodone	
		Paroxetine	
		Propafenone	
		Risperidone	
		Tamoxifen	
		Timolol	
		Tramadol	
		Venlafaxine	

and utility of various medications that might be used in a pain population.

METHODS

Participants and Procedure

The study was reviewed and approved as a retrospective analysis by Aspire Institutional Review Board (IRB), a commercial IRB with central and local coverage, and comprised 104 consecutive patients from a large pain clinic located in Louisiana. Pharmacogenetic testing was carried out on new patients, with chronic pain, entering the clinic to determine phenotypic metabolizing abnormalities in the clinic population as an aid in planning pain treatment. Samples were collected of new patients entering the clinic between the last week of November 2012 and the first week of February 2013. Pharmacogenetic testing was specifically conducted for CYP2B6, CYP2C19, CYP2D6, or UGT2B15 utilizing a noninvasive, saliva-based test.[13] The choice of which marker to test for was determined by clinical decision-making, so not every patient was tested across all four genetic markers. Results were categorized by phenotype, including extensive (EM; normal), intermediate (IM), poor (PM), or ultrarapid (UM) metabolizers for each of the pharmacogenetic markers tested.

RESULTS

The study consisted of 61 men (58.7%) as well as 41 women (39.4%), with 2 patients (1.9%) not reporting gender. The average age of participating subjects was 46.7 years (range = 23–83, SD = 11.5 years). In total, 388 tests were conducted. Across these tests, 164 (42.3%) individual tests were EM (normal), 99 (25.5%) individual tests were IM, 28 (7.2%) individual tests were UM, and 27 (7.0%) individual tests were PM. An additional 70 (18%) exhibited indeterminate results from inadequate DNA samples or unknown polymorphisms.

In total, only 3 patients (3.8%) had genetic patterns as EM (normal) for all four genetic tests performed. Comparatively, 48.4% of the known samples ($n = 154/318$ specimens) exhibited at least one polymorphism. If patients with indeterminate results are included, nearly 40% of the total samples exhibited abnormal findings on one of the four genetic tests. In addition, having a polymorphism in more than one tested enzyme was common. Whereas 37.2% ($n = 29$) had one abnormal gene of the four tested, 25.6% ($n = 20$) had two, and 28.2% ($n = 22$) had three abnormalities. Abnormalities in all four genetic tests were found in 5.1% ($n = 4$) of patients. Specific gene findings, metabolism type by gene, and pertinent haplotype findings per gene are discussed below.

TABLE 2. Results of Individual Genetic Testing and Reporting of Predominant Haplotype Findings

Gene	Metabolism type	Frequency (%)	Predominant haplotypes (frequency)
CYP2B6	EM	47 (59.5)	*1/*1 (29); *1/*5 (14); *1/*4 (2)
	IM	25 (31.6)	*1/*6 (19); *5/*6 (5); *1/*9 (1)
	PM	7 (8.9)	*6/*6 (7)
	UM	0 (0)	NA
CYP2C19	EM	41 (51.2)	*1/*1 (41)
	IM	18 (22.5)	*1/*2 (14); *2/*17 (4)
	PM	2 (2.5)	*2/*2 (1); *2/*8 (1)
	UM	19 (23.8)	*1/*17 (18); *17/*17 (1)
CYP2D6	EM	58 (73.4)	*1/*4 (13); *1/*1 (10); *1/*2 (10); *1/*41 (5)
	IM	9 (11.4)	*4/*41 (3); *41/*9 (2); *17/*17 (1); *17/*41 (1); *4/*9 (1); *41/*5 (1)
	PM	3 (3.8)	*4/*4 (3)
	UM	9 (11.4)	*1/*2 (6); *1/*2×N (1); *1×N/*2 (1); *2/*2×N (1)
UGT2B15	EM	18 (22.5)	*1/*1 (18)
	IM	47 (58.8)	*1/*2 (47)
	PM	15 (18.8)	*2/*2 (15)
	UM	0 (0)	NA

For the 79 tests of CYP2B6, 47 (59.5%) were EM (normal), followed by 25 (31.6%) IM, and 7 (8.9%) PM (see Table 2 for full details). For the 80 tests of CYP2C19, 41 (51.2%) were EM (normal), 19 (23.8%) were UM, an additional 18 (22.5%) were IM, and 2 (2.5%) of the samples were PM. A total of 79 tests of CYP2D6 were conducted, with 58 (73.4%) exhibiting EM (normal), an additional 9 (11.4%) each for IM and UM, and the remaining 3 (3.8%) were PM. Finally, 80 samples were tested for UGT2B15 and resulted in 18 (22.5%) EM (normal), 47 (58.8%) IM, and 15 (18.8%) PM.

DISCUSSION

In this brief report, the experience of one expert-level pain practice is described, wherein the clinical decision was made to perform pharmacogenetic testing on all new patients as part of routine testing. This is done at a time when many clinicians feel underprepared and ill equipped to implement PGT into their practices while nonetheless recognizing its importance.[14] The actual incidence of abnormal PGT results was nearly 40%, but did not rise to the level seen in a recently published report of chronic

pain patients on high doses of opioids, wherein that study found 83% of patients having CYP450 defects compared with 20–30% of the general population.[15] Other sources, however, found results similar to ours with regards to rates of genetic polymorphisms in pain patients.[16] It is recognized that these findings may represent an unusual occurrence based on potential peculiarities of this practice (limiting the generalizability to other pain clinic samples). The possibility that there is a regional or other explanation that may impact these results can only be ruled out with a prospective study performed on a randomly selected sample from a larger group of sites. Indeed, evidence is growing that race and ethnicity play a role in the prevalence of polymorphism rates for CYP450 enzymes and opioid metabolism.[17,18] In the specific area of Cajun genetics, there have been published reports of increased genetic risks for Tay-Sachs disease in those of French ancestry, but there has been nothing published to date regarding opioid metabolism issues in this culture.[19] Nevertheless, the relatively common occurrence of abnormal metabolizers is likely to be found in expert-level pain clinic patients; therefore, PGT should be on the "radar screen" for expert-level pain clinicians.

Patients referred to expert-level pain practices are complex; such practices exist to provide diagnostic and treatment interventions for patients who fail to thrive on any or all of the 4As of pain management. Further referrals can be prompted by unexpected UDT findings suggestive of diversion or abuse, aberrant behaviors, or the possibility of pseudoaddiction.[20–22] Although the latter explanation has been incorrectly taught and overly and too readily applied to explain away aberrant behaviors historically, it is nevertheless a common experience for pain clinicians that "bad actors" receiving less expert care often settle down and make functional and other gains in their care when the patient, their pain diagnosis, and their unique needs are better understood and addressed.[23] Pharmacogenetic abnormalities may be among the ways in which these patients differ from those who are afforded relief and improve on more typical regimens. Furthermore, these patients' failure to obtain analgesia on typical doses or regimens may indeed lead to them being prescribed more complex regimens, with multiple agents, that may only serve to amplify the impact of being an intermediate metabolizer. An example is when an inhibitor to a key pathway is added to a prodrug-based opioid regimen, thereby rendering the opioid even less effective or worsening toxicity. It is indeed a complex clinical picture, one that could, perhaps, be overcome with a series of drug rotations. However, appreciation for the patient's phenotypic status, even while adding the cost of the test to their care, might in the end speed up and render safer the process of finding the right regimen for individual patients, leading to improved outcomes and perhaps cutting overall costs.

With any newer technology in health care, discussion of cost weighed against potential benefit is needed. A genetic polymorphism may simply be an indicator of differences among people and may not represent worrisome or clinically meaningful data. In the case of the four markers discussed herein, as well as other targets, there is an emerging understanding that some genetic polymorphisms can significantly impact on the safety and efficacy of medication choices. Although genetics do not wholly explain adverse drug reactions (ADRs), they may play an important role in some cases, and recent data show that ADRs led to 20% higher death rates, 8% increases in length of hospital stays, and increased total Medicare (20%), drug (9%), and laboratory costs (3%) compared with patients not experiencing ADRs in a study of over 8 million Medicare patients.[24] For genetic testing, researchers have suggested that PGT is becoming increasingly affordable as technologies advance, and call for their costs to be weighed against ADRs, reduced hospitalizations, medication costs, the benefits of testing compared with empiric treatment, and overall disease burden.[25] A recent analysis showed that retrospective pharmacogenetic testing was able to predict higher health care utilization and costs in a psychiatric population.[26] In a prospective fashion for the specific case of CYP2D6 and CYP2C19, research has shown that identifying PM and UM led to significant reductions in health care costs for psychiatric populations.[27] Finally, two recent reviews of economic analyses regarding pharmacogenetics showed that evidence is becoming more robust in support of its use, but do call for more randomized trials.[28,29]

There is a recognized need for a prospective study on a larger sample of randomly selected patients from multiple geographic areas in an attempt to replicate and improve the generalizability of these results. Prior to the accumulation of further data and empirical reports, perhaps expert consensus on the use of PGT may be sought through a guideline panel or other body. PGT can add to the up-front cost of care, yet it may also offset its cost through the avoidance of aborted and failed medication trials and/or patient experiences of adverse medication events. The benefits of its use must be balanced against such costs. Despite these limitations, the findings herein are food for thought for the pain clinician as one of many variables to consider when patients fail to respond in expected fashion, especially in the 4As domains discussed above.

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