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New Pharmacogenetic Options for Managing Pain With Comorbid Psychiatric Conditions

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Clinical Scenario

A 51-year-old man presents to your practice for pain management. Medical records show he has well-established degenerative disk disease. Evaluation of personal and family histories, behavioral aberrancies, Prescription Drug Monitoring Program, physical assessment, and a urine drug test reveal untreated moderate depression and prominent anxiety but no other risk factors for controlled substance misuse. He takes a 120-mg morphine-equivalent dose of oxycodone daily; however, pain is not well controlled and functioning is not optimal.

What is next? Certain antidepressants may be effective adjuvants to help control pain symptoms as well as depression.¹ Low-dose benzodiazepines could be a short-term bridge for anxiety while awaiting anxiolysis from antidepressant therapy. Opioid rotation may improve pain response if you suspect that tolerance to oxycodone has developed.² Given the potential for adverse polypharmacy and inefficacy, how can pharmacogenetic testing help you tailor and optimize your clinical decisions for this patient?

Introduction

Genetics plays a major role in human health. Since the human genome was decoded in 2001, the era of genomic medicine has flourished and new biomedical applications continue to emerge.³ It is now understood that genetics can influence predisposition to specific pain conditions,^{4,5} as well as response to certain analgesics.⁶ Pharmacogenetics (or pharmacogenomics) describes the interplay between drug response and a patient's unique genetic makeup. Clinicians are increasingly adopting this facet of personalized medicine.⁷

Pharmacogenetics predicts how an observed drug response may deviate from expectation due to variations (or polymorphisms) in genes associated with drug pharmacology pathways. Pharmacodynamic

genes encode proteins involved in a drug's therapeutic action and adverse events, such as receptors targeted by drugs.⁸ Pharmacokinetic genes encode proteins that affect the *amount* of drug and metabolite(s) available for pharmacodynamic action, such as drug-metabolizing enzymes (DMEs) including cytochrome P450 (CYP) enzymes, and drug transporters.⁸ Genetic variations in pharmacokinetic and pharmacodynamic genes that cause changes to protein function may translate to differences in clinical response to certain medications. Pharmacogenetic testing identifies patients who carry such variations and can help clinicians understand and ameliorate unexpected toxicity or poor efficacy in patients. If used preemptively, testing can help identify patients that need alternative medications or dosing schedules.

Pharmacotherapy Considerations for Patients With Comorbid Pain and Psychiatric Disorders

Patients with chronic pain have a 4-fold higher rate of depression, a 2.5-fold higher rate of anxiety, and a 1.5-fold higher rate of substance use disorders than the general population.⁹ Pharmacotherapy in patients with comorbidities often includes analgesics given concomitantly with psychotropic drugs, some of which also serve as adjuvant analgesics. Because multiple concomitant medications are often the rule—not the exception—drug–drug interactions are a serious concern.¹⁰ Among the 16,000 opioid overdose deaths identified in 2010 in the United States, benzodiazepines, antidepressants, and anticonvulsants were coprescribed in 30%, 13%, and 7% of the cases, respectively.¹¹

Therapeutic responses to opioids and psychotropics are often unpredictable, exaggerated, and/or suboptimal.¹² For example, opioid dose requirements can vary by as much as 40-fold in patients with chronic pain.¹³ Initial antidepressant therapy alleviates symptoms in approximately 30% of depressed patients, whereas almost 1 in 3 patients are symptomatic even after 4 successive medication trials.¹⁴ Patients with comorbidities are often at higher risk for poor pain¹⁵ and psychiatric¹⁶ outcomes, which can compound treatment challenges. Higher rates of disability,¹⁷ health care utilization,¹⁸ and unemployment¹⁹ place additional economic burdens on comorbid patients and the health care system. A patient's psychiatric history also can increase the risk for opioid misuse.²⁰ Thus, clinicians treating patients with comorbidities must carefully navigate treatment selection and dosing decisions.

Pharmacogenetic-Based Drug Selection and Dosing

Pharmacogenetics enables tailored prescribing of opioid and psychotropic medications, and may help clinicians minimize treatment failures and serious side effects from trial-and-error strategies. Several clinically actionable genotypes have been identified that are important for safe response to pain and psychotropic medications (Table). The literature is most extensive for pharmacokinetic DME targets, and many of these drug–gene pairs now have guidelines^{21,22} and FDA labeling²³ recommendations. For example, CYP2D6 metabolism status is important when codeine, tramadol, or oxycodone is prescribed.²⁴

There are some key pharmacodynamic genes with sufficient clinical evidence for actionable polymorphisms when prescribing certain pain and psychiatric medication also listed in the Table. The following is a summary of these genes and a select list of supporting references:

- Carriers of the HLA-B *1502 polymorphism are at higher risk for potentially fatal hypersensitivity reactions and may need to avoid certain anticonvulsants.²⁵⁻²⁷
- Patients with the HTR2C-759C (rs3813929) polymorphism may be protected from antipsychotic-induced weight gain, especially with olanzapine or clozapine.^{28,29}
- Patients with MTHFR polymorphisms (C677T, A1298C) activate dietary folate poorly, and may have an improved antidepressant response with L-methylfolate supplementation.^{30,31}
- Carriers of OPRM1 A118G may have inadequate pain relief with standard fentanyl or morphine doses, yet may be better candidates for naltrexone therapy to treat alcohol addiction.^{32,33}

Table. Actionable Pharmacokinetic and Pharmacodynamic Genes for Personalizing Treatment for Comorbid Pain and Psychiatric Disorders

	Gene (Markers)	Clinical Role	Potential Clinical Phenotype	Drugs With Genetic Associations
DMEs	CYP enzyme family (various)	Hepatic drug metabolism	Unexpected parent/metabolite levels and drug response	Antidepressants, opioids, NSAIDs, antipsychotics, benzodiazepines
	UGT2B15 (*2)			Benzodiazepines (eg, lorazepam, oxazepam)
Drug Receptors	DRD2 (-141C Ins/Del)	Binding site for antipsychotic drugs	Reduced antipsychotic response	Antipsychotics (eg, risperidone, clozapine, olanzapine)
	HTR2C (rs3813929)	Serotonin receptor affecting appetite	Less antipsychotic-induced weight gain	Antipsychotics (eg, clozapine, olanzapine)
	OPRM1 (A118G)	Binding site for opioid drugs	Need for higher opioid doses	Opioids (eg, morphine, fentanyl)
Auxiliary Pharmacogenes	COMT (Val158Met)	Inactivates dopamine and norepinephrine	Need for nonstandard opioid doses	Opioids (eg, morphine, fentanyl)
	HLA-B (*1502)	Mediates acquired immune response	Higher risk for drug-induced hypersensitivity	Anticonvulsants (eg, carbamazepine, oxcarbazepine, lamotrigine, phenytoin)
	MTHFR (C677T, A1298C)	Activates folate and impacts mood	Improved response to L-methylfolate	SSRIs/SNRIs

CYP, cytochrome P450; DMEs, drug-metabolizing enzymes; NSAIDs, nonsteroidal anti-inflammatory drugs; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors

- Carriers of COMT Val158Met may require atypical morphine dosing for optimal analgesia and fewer side effects.^{34,35}
- Carriers of the DRD2 -141C Ins/Del polymorphism may have an inadequate response to antipsychotics, particularly risperidone, clozapine, or olanzapine.^{36,37}

Frequency of Genetic Variation

Current evidence demonstrates that polymorphisms in key pharmacokinetic and pharmacodynamic genes may affect response to certain medications used during treatment of patients with pain and psychiatric disorders. An important consideration for the prescribing clinician is to understand how frequently genetic variation can occur in individuals. Much of the published literature examines frequency of variation in populations for a single gene. However, in patients receiving polypharmacy, a constellation of genes may be involved in mediating observed clinical response, and therefore, frequency data from single-gene studies may provide incomplete information. A recent study tested a heterogenous patient population (N=1,143) across 3 enzyme genes (CYP2D6, CYP2C19, CYP2C9), and found that the majority (52%) of patients have polymorphisms in 2 of 3 genes tested. These data suggest that genetic variation is common if examined across multiple genes.³⁸

Furthermore, data from a retrospective analysis of specimens submitted for genetic testing to a large specialty laboratory support these findings.³⁹ In the analysis, a subset of patients (N=1,807) were identified who received treatment at specialty pain practices and were tested across 9 genes (CYP2D6, CYP2C9, CYP2C19, MTHFR, OPRM1, COMT, CYP3A4/5, UGT2B15, CYP2B6). This specific combination of genes may be relevant for a polypharmacy regimen involving opioids, antidepressants, and benzodiazepines. Results demonstrate that 75% of patients were variant at the phenotype level for between 3 and 5 genes. Moreover, approximately 10% were phenotypically variant for between 6 and 8 genes (Figure). Thus, phenotype variation appears to be common in this patient subset when tested across these 9 genes. Phenotypic variation may lead to poor treatment efficacy and/or compound the risk for drug–drug interactions and serious side effects. Pharmacogenetic testing may help the clinician identify variant patients in order to customize their therapy to maximize response and minimize toxicity.

Clinical Scenario Revisited

Pharmacogenetic testing of genes involved in response to opioids, antidepressants, and benzodiazepines may help you tailor treatment for this patient. For example, the patient may be a CYP2D6 poor metabolizer, which may account for his poor pain control with oxycodone.⁴⁰ The patient's analgesia may improve if switched to an opioid that bypasses CYP2D6 metabolism (ie, morphine, hydromorphone, oxymorphone, tapentadol).⁴⁰ Antidepressants that bypass the CYP2D6 metabolic pathway may be better options as well. COMT and OPRM1 genotyping may help you determine initial dosing of alternative

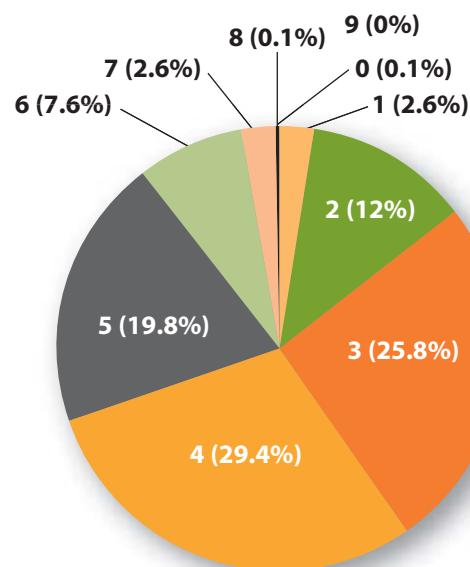


Figure. Number of phenotype variants in patient subset (N=1,807) tested across 9 genes (CYP2D6, CYP2C19, CYP2C9, CYP2B6, CYP3A4/5, UGT2B15, COMT, OPRM1, MTHFR) involved in response to opioids, benzodiazepines, and antidepressant polypharmacy.

Patients receiving treatment in specialty pain practices and genotyped for 9 genes (N=1,807) were assigned a predicted phenotype per gene. Variants denote patients with phenotypes not corresponding to the normal (ie, wild type) phenotype for a given gene. Specimens were submitted to Millennium Health from July 2012 to September 2014. Deidentified data were retrospectively analyzed as part of an IRB-approved protocol (#52013-I-13002; Aspire, Santee, California). Tests were ordered by multiple providers across the US according to patient clinical and medical necessity. Multiple factors influence variation frequencies, including patient ethnicity, and number and specific combination of genes tested. Thus, caution should be used if extrapolating these data to other gene combinations or the general population.

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Based on reference 39.

opioids if considering a medication switch.³²⁻³⁵ UGT2B15 testing may indicate that the patient is a reduced-function metabolizer, which can lead to an exaggerated response to certain benzodiazepines, which necessitates atypical dosing or avoiding these medications.⁴¹ Finally, if the patient carries MTHFR polymorphisms, L-methylfolate supplementation may augment the patient's antidepressant response.^{30,31} Thus, pharmacogenetic information can help the clinician make rational medication and dosing decisions for this patient with comorbid pain and psychiatric disorders to optimize treatment outcomes.

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