

Pharmacogenetic guidance: individualized medicine promotes enhanced pain outcomes

Lisa Lynn Dragic¹

Erica L Wegrzyn²

Michael E Schatman³⁻⁵

Jeffrey Fudin^{2,6}

¹Central Arkansas Veterans Healthcare System, Little Rock, AR, USA;

²Department of Pharmacy, Albany Stratton VA Medical Center, Albany, NY, USA; ³Research and Network Development, Boston Pain Care, Waltham, MA, USA; ⁴Public Health and Community Medicine, Tufts University School of Medicine, Boston, MA, USA;

⁵Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, MA, USA; ⁶Scientific and Clinical Affairs, Remitigate, LLC, Delmar, NY, USA

Abstract: The use of pharmacogenomics has become more prevalent over the past several years in treating many disease states. Several cytochrome P450 enzymes play a role in the metabolism of many pain medications including opioids and antidepressants. Noncytochrome P450 enzymes such as methylenetetrahydrofolate reductase (MTHFR) and catechol-*O*-methyl transferase (COMT) also play a role in the explanation of opioid dosage requirements as well as in response to certain antidepressants. We present the case of a patient with reduced *COMT* and *MTHFR* expression treated with leucovorin 10 mg daily for the management of chronic pain. The use of leucovorin in this patient decreased pain scores, which were clinically significant and increased functionality. This case demonstrates the importance of pharmacogenetics testing in patients, as this can help direct providers to better therapeutic options for their patients.

Keywords: pharmacogenetic, depression, pain, MTHFR, COMT, methyl tetrahydrofolate reductase, catechol-*O*-methyltransferase

Introduction

Pharmacogenetics (PGT) plays an important role in several disease states including pain management and mental health disorders. The use of pharmacogenomics has become more prevalent over the past several years in treating various disease states, and over 150 drug manufacturers' inserts include statements on dosing depending on these parameters. Several cytochrome (CYP) P450 enzymes play a role in the metabolism of many pain medications, including opioids and antidepressants. Genetic phenotypes vary among worldwide populations and even within populations.¹ This phenomenon is known as polymorphism. Aside from CYP450 polymorphisms, there are many important genetic factors that affect response to and side effects of various medications that are commonly used in pain patients. This is especially important in patients with long-term pain when considering that various mental health disorders are common.² Examples of nonCYP450 polymorphisms include methylenetetrahydrofolate reductase (MTHFR) and catechol-*O*-methyl-transferase (COMT), both of which play an important role in opioid and antidepressant response. We present a unique and interesting case of a patient with reduced *COMT* and *MTHFR* genes and the impact of initiating leucovorin. Ethical considerations for including PGT in the differential are discussed in terms of cost justification and outcomes.

Correspondence: Jeffrey Fudin
Scientific and Clinical Affairs, Remitigate
LLC, 357 Delaware Avenue, #124,
Delmar, NY 12054, USA
Tel +1 518 558 5651
Email jeffrey.fudin@remitigate.com

Table 1

Examples of medications	Enzyme	Metabolite
Citalopram	2C19, 3A4, 2D6	Desmethylcitalopram
Venlafaxine	2D6	O-desmethylvenlafaxine
Bupropion	2B6	Hydroxybupropion

Background

PT is a 48-year-old man with a past medical history significant for attention-deficit hyperactivity disorder (ADHD), obstructive sleep apnea, fibromyalgia, posttraumatic stress disorder, and chronic low-back pain. The patient presented in October 2016 with worsening fibromyalgia pain and previous extreme sensitivity to antidepressants as outlined later. Prior to the patient's visit to a comprehensive pain clinic, the patient was started on duloxetine, and after 5 days the patient reported a "debilitating headache and hangover effect." The patient also reported similar side effects to venlafaxine, citalopram, sertraline, bupropion, and mirtazapine.

Because of the patient's reactions to multiple medications, PT was sent for a PGT by saliva swab. PT was tested for 2C19, 2D6, 3A4/5, *MTHFR*, and *COMT*, all of which are responsible for the metabolism of many medications.^{3,4} For a summary of results, see Table 1.

PGT results

PGT testing yielded the following: *COMT* – reduced activity, *MTHFR* – reduced activity, CYP3A4 and CYP3A5 – intermediate metabolizer, CYP2C19 – normal metabolizer, CYP2D6 – normal metabolizer, and UGT2B15 – normal metabolizer.

Role of COMT and MTHFR

The patient exhibited reduced *COMT* activity, specifically the expression of the VAL158MET genotype. *COMT* is an enzyme that is responsible for the breakdown of serotonin, dopamine, norepinephrine, and other common neuroamines within neuronal junctions.^{5–7} The VAL158Met allele is associated with low *COMT* activity, which corresponds to increased concentrations of dopamine and norepinephrine in the cortical region.^{5–7} PT was also receiving methylphenidate, which blocks the reuptake of norepinephrine and dopamine into presynaptic neurons, resulting in increased dopaminergic and noradrenergic activity in the prefrontal cortex. We note that PT also exhibited reduced *MTHFR* activity, specifically the 677T and A1298C genotypes. *MTHFR* is responsible for converting 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, and 5-methyltetrahydrofolate is the predominant

circulating form of folate.⁸ *MTHFR* C677T polymorphism is associated with a reduction in the bioavailability of folate and folate metabolites. Thus, we expected PT to demonstrate a decreased ability to convert folic acid to its active form, essentially mimicking low dietary folate intake.⁸ Not only have reduced folate levels been linked to depression, but also to attention deficit disorder.^{8–10}

At PT's subsequent pain management visit in October 2016, he reiterated his extreme sensitivity to antidepressants and insufficient response to methylphenidate both for depression and ADHD. Theoretically, PT should have exhibited an increased response to methylphenidate due to reduced *COMT* activity; however, there is a possibility that the patient may have uncontrolled attention deficit disorder despite treatment due to reduced levels of usable folate. *MTHFR* activity is associated with poor or limited response to antidepressants, pain medications, and methylphenidate.¹⁰ Therefore, we hypothesized that PT could benefit from the addition of folate supplementation such as L-methylfolate or leucovorin for pain, depression, and perhaps ADHD.¹⁰

Folate supplementation

L-Methylfolate is the active form of folate, and is the only form of folate that crosses the blood–brain barrier.¹⁰ Studies suggest that the use of L-methylfolate as an adjunctive agent to specific serotonin reuptake inhibitor and serotonin norepinephrine reuptake inhibitor treatment is associated with improved depression treatment outcomes.¹⁰ Additionally, supplementation of L-methylfolate may provide increased efficacy of methylphenidate.¹⁰

Since L-methylfolate was not a formulary item within the institution at which PT was being treated, the patient was started on leucovorin (folinic acid) 10 mg PO each morning for folate supplementation in November 2016. Leucovorin is the active form of folate and does not require *MTHFR* for activation. Possible side effects of leucovorin include neuropathic pain and zinc depletion; therefore, we provided him with zinc sulfate 220 mg PO every evening.

Prior to initiation of leucovorin, PT reported a pain level of 9 out of 10 on a visual analog scale of 0–10, with 0 signifying no pain and 10 representing the worst pain possible. Just 1 week following the initiation of leucovorin, the patient reported his pain level to be 2–3 out of 10. He reported feeling "much better than before and was sharing his positive results with his friends in the medical field and was very grateful for the genetics testing." Eight months later, he remains stable with regard to his pain, depression, and ADHD. He also reported increased functioning with daily activities.

Although the clinical implications of this case are quite evident, the ethical issues associated with it are both obvious and subtle. First, and perhaps foremost, PGT should be performed in all cases in which patients demonstrate a combination of both nonresponsiveness and hypersensitivity to numerous medications. Unfortunately, in the United States, PGT is underutilized, with much of this failure to regularly use such technology due to insurers' refusal to cover its costs. This failure has been empirically demonstrated to reduce patients' willingness to utilize PGT, irrespective of their interest in such tests.¹¹ Fortunately, the Veterans' Affairs Medical System through which PT was treated has the wisdom to recognize that cost containment is not necessarily synonymous with cost efficiency.

Second, while CYP450 polymorphisms seem to receive considerable attention due to their formidable impact on opioid response, clinicians (and payers) need to recognize that a broad range of potential polymorphisms should not be ignored. In the case of PT, he was determined to be a normal metabolizer of CYP2D6 – the most common CYP P450 polymorphism.¹² “Simple” PGT testing is not necessarily “thorough” PGT, with this case serving as evidence that numerous potential polymorphisms should be considered when patients are nonresponsive or hypersensitive to multiple therapeutic agents.

Finally, PT's good fortune to be treated by open-minded clinicians should not be underestimated. As a sufferer of long-term pain, many hospitals would not have done their due diligence by providing him with a comprehensive PGT panel. Patients with chronic pain, for myriad unfortunate reasons, are expected to respond positively to whatever pharmacologic intervention is initially provided. Those who do not do so are often stigmatized and provided with pejorative labels such as “drug-seekers.”¹³ We posit that although all patients with disease states deserve precision medicine approaches such as that received by PT, the stigmatization and marginalization of patients with the disease of chronic pain and criticism for random morphine equivalent daily dose limits in this unfortunate era of frank opiophobia make consideration of the comprehensive use of PGT even more crucial if their condition is to be treated from an optimally ethical perspective.

Consent

The patient has provided written informed consent for the case details to be published.

Disclosure

Dr Schatman would like to disclose that he is a consultant for Depomed. Dr Fudin discloses the following: Astra Zeneca (Speakers Bureau), Daiichi Sankyo (Advisory Board), Egalet (consultant, Advisory Board), Quest Labs (Advisory Board), Remitgate, LLC (Owner). The authors report no other conflicts of interest in this work.

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