



Abstract: 6222

Scientific Abstracts &gt; Acute Pain

# PHARMACOGENOMICS OF OPIOID CONSUMPTION AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

Rebecca Cox, Austin Collins, Emily Demaio, Rebecca Haley, Greg Darville, Nicole Greene, John Xerogeanes  
MedStar

## Introduction

According to the Centers for Disease Control and Prevention (CDC), the United States is in the midst of an opioid epidemic. Still, there remains a paucity of research regarding how one's individual genetic composition may affect opioid consumption patterns. This study analyzed patients who underwent anterior cruciate ligament reconstruction (ACLR) to identify if a relationship between patient's pharmacogenetics and their postoperative opioid consumption existed. This study seeks to illustrate the benefits of pharmacogenomic testing via non-invasive, low-cost buccal swabs to identify one's specific pharmacokinetic and pharmacogenomic responses to opioid medications. This knowledge will have the potential to shape the future of pain management by guiding physicians to create individualized pain management plans with unique drug regimens and educational content specific to each patient's needs.

## Materials and Methods

The study is approved through the Institutional Review Board (IRB) of Emory University (IRB00002086). All participants provided informed consent prior to participation. Eligible subjects were contacted by phone via study personnel. If they elected to participate, subjects had the option to sign the consents electronically on their personal electronic device utilizing Research Electronic Data Capture (REDCap, Vanderbilt University, Nashville, TN, USA) or physically when they presented for buccal swab collection. Identifiers were stripped prior to providing specimens and data to our external collaborators and statisticians.

One hundred patients aged 18-50 years old were divided into cohorts based on their opioid tablet consumption patterns. Cohorts were defined as non, low, middle, high, and maximum opioid users. Participants' DNA was analyzed for genes relating to pharmacodynamics and pharmacokinetics including CYP3A4, CYP2D6, CYP3A5, OPRM1, and COMT.

## Results/Case Report

The average age of study participants was 31 with 44% male and 56% female. When analyzing CYP2D6, there were differences identified in the number of opioid tablets consumed between the poor metabolizers and the normal metabolizers ( $p < 0.05$ ). For COMT, there were differences noted in the number of opioid tablets consumed between the high metabolizers and the low metabolizers ( $p < 0.05$ ). CYP3A4, CYP3A5, and OPRM1 were not found to have a significant effect on the number of tablets consumed.

## Discussion

Both COMT and CYP2D6 were associated with higher metabolism rates and increased opioid usage within the study cohorts. This finding has the potential to shape the future of orthopedic care by guiding surgeons to create individualized postoperative pain management plans with unique drug regimens and educational content specific to each patient's needs. However, further research is required to better understand the effect of a patient's individual genetic composition on opioid consumption patterns.

## References

1. CDC Grand Rounds: Prescription Drug Overdoses — a U.S. Epidemic. Accessed August 29, 2023. <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6101a3.htm>
2. Opioid use, misuse, and abuse in orthopaedic practice. *Surg AAOO*. Published online 2015.
3. Morris BJ, Mir HR. The opioid epidemic: impact on orthopaedic surgery. *J Am Acad Orthop Surg*. 2015;23(5):267-271. doi:10.5435/JAAOS-D-14-00163
4. Kee JR, Smith RG, Barnes CL. Recognizing and Reducing the Risk of Opioid Misuse in Orthopaedic Practice. *J Surg Orthop Adv*. 2016;25(4):238-243.
5. Hah JM, Bateman BT, Ratliff J, Curtin C, Sun E. Chronic Opioid Use After Surgery: Implications for Perioperative Management in the Face of the Opioid Epidemic. *Anesth Analg*. 2017;125(5):1733-1740. doi:10.1213/ANE.0000000000002458
6. Squassina A, Manchia M, Manolopoulos VG, et al. Realities and expectations of pharmacogenomics and personalized medicine: impact of translating genetic knowledge into clinical practice. *Pharmacogenomics*. 2010;11(8):1149-1167. doi:10.2217/pgs.10.97
7. Hamburg MA, Collins FS. The path to personalized medicine. *New England Journal of Medicine*. 2010;363(4):301-304. - Google Search. Accessed March 1, 2023. <https://www.google.com/search?q=Hamburg+MA%2C+Collins+FS.+The+path+to+personalized+medicine.+New+England+Journal+of+Me+304.&oq=Hamburg+MA%2C+Collins+FS.+The+path+to+personalized+medicine.+New+England+Journal+304.&aqs=chrome..69i57.255j0j4&sourceid=chrome&ie=UTF-8>
8. Whirl-Carrillo M, McDonagh EM, Hebert JM, et al. Pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther*. 2012;92(4):414-417. doi:10.1038/clpt.2012.96
9. Marino M, Jamal Z, Zito PM. Pharmacodynamics. In: *StatPearls*. StatPearls Publishing; 2022. Accessed March 1, 2023. <http://www.ncbi.nlm.nih.gov/books/NBK507791/>
10. Holland-Frei *Cancer Medicine*. 6th ed. BC Decker; 2003.
11. Franconi F, Campesi I. Pharmacogenomics, pharmacokinetics and pharmacodynamics: interaction with biological differences between men and women. *Br J Pharmacol*. 2014;171(3):580-594. doi:10.1111/bph.12362
12. Shafer SL, Varvel JR. Pharmacokinetics, pharmacodynamics, and rational opioid selection. *Anesthesiology*. 1991;74(1):53-63. doi:10.1097/0000542-199101000-00010
13. Gudin J. Opioid Therapies and Cytochrome P450 Interactions. *J Pain Symptom Manage*. 2012;44(6):S4-S14. doi:10.1016/j.jpainsymman.2012.08.013
14. Smith HS. Opioid metabolism. *Mayo Clin Proc*. 2009;84(7):613-624. doi:10.1016/S0025-6196(11)60750-7
15. Guengerich FP. Cytochrome P450 and Chemical Toxicology. *Chem Res Toxicol*. 2008;21(1):70-83. doi:10.1021/tx700079z
16. Denisov IG, Makris TM, Sligar SG, Schlichting I. Structure and chemistry of cytochrome P450. *Chem Rev*. 2005;105(6):2253-2277. doi:10.1021/cr0307143
17. Söderberg Löfdal KC, Andersson ML, Gustafsson LL. Cytochrome P450-mediated changes in oxycodone pharmacokinetics/pharmacodynamics and their clinical implications. *Drugs*. 2013;73(6):533-543. doi:10.1007/s40265-013-0036-0

18. Deodhar M, Turgeon J, Michaud V. Contribution of CYP2D6 Functional Activity to Oxycodone Efficacy in Pain Management: Genetic Polymorphisms, Phenoconversion, and Tissue-Selective Metabolism. *Pharmaceutics*. 2021;13(9):1466. doi:10.3390/pharmaceutics13091466
19. Liukas A, Kuusniemi K, Aantaa R, et al. Elimination of intravenous oxycodone in the elderly: a pharmacokinetic study in postoperative orthopaedic patients of different age groups. *Drugs Aging*. 2011;28(1):41-50. doi:10.2165/11586140-000000000-00000
20. Bromley CM, Close S, Cohen N, et al. Designing pharmacogenetic projects in industry: practical design perspectives from the Industry Pharmacogenomics Working Group. *Pharmacogenomics J*. 2009;9(1):14-22. doi:10.1038/tpj.2008.11
21. Zhou Y, Ingelman-Sundberg M, Lauschke VM. Worldwide Distribution of Cytochrome P450 Alleles: A Meta-analysis of Population-scale Sequencing Projects. *Clin Pharmacol Ther*. 2017;102(4):688-700. doi:10.1002/cpt.690
22. Lynch T, Price A. The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. *Am Fam Physician*. 2007;76(3):391-396.
23. Zwisler ST, Enggaard TP, Noehr-Jensen L, et al. The Hypoalgesic Effect of Oxycodone in Human Experimental Pain Models in Relation to the CYP2D6 Oxidation Polymorphism. *Basic Clin Pharmacol Toxicol*. 2009;104(4):335-344. doi:10.1111/j.1742-7843.2009.00378.x
24. Samer C, Daali Y, Wagner M, et al. Genetic polymorphisms and drug interactions modulating CYP2D6 and CYP3A activities have a major effect on oxycodone analgesic efficacy and safety. *Br J Pharmacol*. 2010;160(4):919-930. doi:10.1111/j.1476-5381.2010.00709.x
25. Stamer UM, Zhang L, Book M, Lehmann LE, Stuber F, Musshoff F. CYP2D6 genotype dependent oxycodone metabolism in postoperative patients. *PLoS One*. 2013;8(3):e60239. doi:10.1371/journal.pone.0060239
26. Reyes-Gibby CC, Shete S, Rakvåg T, et al. Exploring joint effects of genes and the clinical efficacy of morphine for cancer pain: OPRM1 and COMT gene. *Pain*. 2007;130(1-2):25-30. doi:10.1016/j.pain.2006.10.023
27. De Gregori M, Garbin G, De Gregori S, et al. Genetic variability at COMT but not at OPRM1 and UGT2B7 loci modulates morphine analgesic response in acute postoperative pain. *Eur J Clin Pharmacol*. 2013;69(9):1651-1658. doi:10.1007/s00228-013-1523-7
28. Rakvåg TT, Ross JR, Sato H, Skorpen F, Kaasa S, Klepstad P. Genetic variation in the catechol-O-methyltransferase (COMT) gene and morphine requirements in cancer patients with pain. *Mol Pain*. 2008;4:64. doi:10.1186/1744-8069-4-64
29. Rakvåg TT, Klepstad P, Baar C, et al. The Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. *Pain*. 2005;116(1-2):73-78. doi:10.1016/j.pain.2005.03.032
30. Candiotti KA, Yang Z, Buric D, et al. Catechol-o-methyltransferase polymorphisms predict opioid consumption in postoperative pain. *Anesth Analg*. 2014;119(5):1194-1200. doi:10.1213/ANE.0000000000000411
31. Huddart R, Clarke M, Altman RB, Klein TE. PharmGKB summary: oxycodone pathway, pharmacokinetics. *Pharmacogenet Genomics*. 2018;28(10):230-237. doi:10.1097/FPC.0000000000000351
32. Li J, Peng P, Mei Q, et al. The impact of UGT2B7 C802T and CYP3A4\*1G polymorphisms on pain relief in cancer patients receiving oxycontin. *Support Care Cancer*. 2018;26(8):2763-2767. doi:10.1007/s00520-018-4130-4
33. Pu J, Wang N, Huang ZK, He XY, Yuan HB. Correlation between gene polymorphism and opioid efficacy in patients with gastric or intestinal cancer. *Eur Rev Med Pharmacol Sci*. 2019;23(21):9393-9410. doi:10.26355/eurrev\_201911\_19432
34. Kim KM, Kim HS, Lim SH, et al. Effects of genetic polymorphisms of OPRM1, ABCB1, CYP3A4/5 on postoperative fentanyl consumption in Korean gynecologic patients. *Int J Clin Pharmacol Ther*.

2013;51(05):383-392. doi:10.5414/CP201824

35. Zwisler ST, Enggaard TP, Mikkelsen S, et al. Lack of association of OPRM1 and ABCB1 single-nucleotide polymorphisms to oxycodone response in postoperative pain. *J Clin Pharmacol*.

2012;52(2):234-242. doi:10.1177/0091270010397729

## Disclosures

No

## Tables / Images

□

□