Can the OPRM1 Gene Predict Risk for Opioid Misuse? A Human Laboratory Examination

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Introduction and Aims: Opioids present a unique challenge because of the need to balance opioid prescribing for pain management with mitigation of risk for opioid-related consequences. There currently exist no robust predictors of opioid misuse risk. This study applied a human abuse potential framework to evaluate associations between OPRM1 genotype and opioid abuse potential phenotype.

Design and Methods: This was a triple-blinded, within-subject, placebo-controlled human laboratory abuse potential trial. Healthy men (N=50) and women (n=50) stayed in a residential unit for 5 days and received oral doses of placebo and hydromorphone (2mg, 4mg, 8mg). Outcomes were standard self-report, observer-ratings, and physiological abuse potential endpoints. Genome-wide association (GWAS) was completed with the Global Screening Array.

Key Findings: SNPs in OPRM1 were significantly associated with several signals of elevated abuse risk, including ratings of HIGH $\geq$60 (p=0.04), Take Again (p=0.03), Enjoying the Drug (p=0.04), and being an opioid responder (p=0.02). Exploratory analysis revealed SNPs on the CLOCK gene were strongly associated with HIGH $\geq$60(p=.0004) and several additional genes showed significant associations. Participant sex did not reliably impact outcomes.

Discussions and Conclusions: Individual differences in opioid response signified different levels of risk for opioid misuse, and results suggest OPRM1 contributes (at least in part) to those differences. This is the first study of this type to be conducted among persons with no preexisting history of problematic opioid use, and these data can inform and advance efforts to prevent development of opioid use disorder, particularly among persons receiving opioid prescriptions.

Implications for Practice or Policy: These data can be used to inform an opioid abuse phenotype, which could be applied in practice to identify persons at elevated risk for opioid misuse prior to the onset of OUD.

Implications for Translational Research: The rigorous phenotyping methodology used here generalizes well to the experimental methods used in preclinical assessments and can support cross-species translation, particularly with regard to the CLOCK gene finding.

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