

Pharmacogenetics of the μ -opioid receptor and the treatment of addictions

Lara A Ray^{1,2†},
James MacKillop² &
Kent E Hutchison¹

[†]Author for correspondence

¹University of Colorado at
Boulder, Department of
Psychology, Boulder, CO,
USA

²Brown University,
Center for Alcohol and
Addiction Studies,
Brown Medical School,
Box G-BH, Providence,
RI 02912, USA

Tel.: +1 401 455 6350;
Fax: +1 401 274 0771;
E-mail: Lara_Ray@
brown.edu

**Evaluation of: Munafò MR, Elliot KM, Murphy MF, Walton RT, Johnstone EC:
Association of the μ -opioid receptor gene with smoking cessation.**

Pharmacogenomics J. (2007) (In Press) [1]. This well-designed study examined short- and long-term outcome data from a large clinical trial comparing nicotine-replacement therapy (NRT) with placebo in order to test the association between the μ -opioid receptor gene and treatment outcomes. In addition to a significant effect of NRT compared with placebo across time periods, analyses revealed a significant genotype \times treatment interaction at 12-week follow-up, such that participants who were homozygous for the A allele were more likely to report smoking abstinence in the NRT condition versus placebo compared with carriers of the G allele. These results did not persist after NRT was discontinued, although its temporal contiguity to treatment suggests it is a true pharmacogenetic effect. Importantly, these findings stand in contrast to previous research in the field. Moreover, the study reported provocative interactions between gender and μ -opioid receptor gene status with regard to long-term treatment outcome, and between abstinence and gender with regard to changes in body mass index. Munafò and colleagues' study has a number of strengths and its overall findings underline the complex ways in which genotype, gender and body mass index may interact in smoking-cessation treatment. The significance of these findings is discussed in the context of pharmacogenetics research in the field of substance-use disorders.

In light of the large observed interindividual variability in clinical response to pharmacotherapies for addictive behaviors, such as nicotine and alcohol dependence, recent research has focused on identifying moderators of medication response, including genetic variants, as a means of optimizing treatments in the future. In a well-designed study, Munafò and colleagues examined the role of a functional polymorphism of the μ -opioid receptor gene (*OPRM1*) in treatment outcomes in a large, double-blind, placebo-controlled trial of nicotine-replacement therapy (NRT) for smoking cessation [1]. Most candidate-gene pharmacogenetic studies to date have focused on genetic factors influencing medication efficacy and toxicity, emphasizing polymorphisms that have an effect on pharmacokinetics (e.g., drug metabolism) or pharmacodynamics (e.g., drug sensitivity) [2]. Based on previous research, Munafò and colleagues selected the A118G single nucleotide polymorphism (SNP) of *OPRM1*, located in position +118 in exon I, whereby a nonsynonymous mutation results in an amino-acid substitution from asparagine to aspartate. This polymorphism has been shown to be functionally significant, with studies suggesting that the SNP affects receptor-binding affinity [3],

messenger RNA and protein yield [4]. At the behavioral level, carriers of the G allele have been found to exhibit greater sensitivity to the subjective effects of alcohol [5], greater relative reinforcement value of nicotine (in women) [6] and greater levels of short-term smoking abstinence to NRT [7]. Taken together, previous studies have suggested that this candidate SNP is functional at molecular and behavioral levels and may be especially relevant to the study of addictive behaviors, given the putative role of the opioidergic system in the reward mechanisms for several substances of abuse, including alcohol and nicotine. Munafò and colleagues examined short- and long-term outcome data from a large clinical trial comparing NRT with placebo to test the association between the *OPRM1* genotype and treatment outcomes in this trial. In addition, the study examined body mass index (BMI) and gender as variables that may predict treatment outcome and may interact with the genotype of interest.

The authors did not put forth specific hypotheses regarding the nature of the relationships among genotype, treatment outcome, BMI and gender. However, based on the literature carefully reviewed in their introduction, it would be reasonable to hypothesize that carriers of the G allele

Keywords: addictions, gender, nicotine-replacement therapy, *OPRM1* gene, pharmacogenetics

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would respond better to NRT, given that they have done so in a study of the short-term effects of NRT [7]. Moreover, given that the G allele has been previously associated with higher reinforcement value of nicotine among women but not men [6], it would be reasonable to hypothesize that the relationship between genotype and treatment outcome would be moderated by gender, with stronger genotype effects expected among female patients. Importantly, this study was double-blind and placebo-controlled, and its large sample size provided the statistical power necessary to test moderators of clinical response to NRT and, ultimately, inform efforts to optimize pharmacological interventions for nicotine dependence.

Results

As would be expected, active NRT was associated with a better treatment outcome compared with placebo across follow-up intervals, with highly significant differences for the first three intervals and a statistical trend-level difference at 8-year follow-up. Analyses regarding the effect of genotype revealed a significant genotype \times treatment interaction at 12-week follow-up, such that participants who were homozygous for the A allele were more likely to report smoking abstinence in the NRT condition versus placebo compared with carriers of the G allele (i.e., AG/GG genotypes). This finding did not persist after NRT was discontinued (at week 12), and its temporal contiguity suggests that it was a true pharmacogenetic effect reflecting a significant interaction between an exogenous agent (i.e., pharmacotherapy) and the endogenous variable (i.e., genotype). In addition, analyses of abstinence rates across treatment conditions (i.e., NRT or placebo) revealed that, among male participants, individuals who were homozygous for the A allele were more likely to report abstinence at each time in follow-up (i.e., 12-week, 26-week, 1-year and 8-year) compared with carriers of the G allele. Conversely, the A \rightarrow G substitution was associated with a higher overall likelihood of abstinence among female participants compared with AA homozygotes. Importantly, the findings for females did not reflect differential response to NRT as a pharmacotherapy, given that these results were found collapsing across the active treatment and placebo conditions.

Analyses regarding BMI indicated that, overall, individuals' BMI increased across follow-up points. Ex-smokers, older participants and individuals of lower socioeconomic status reported

significantly greater increases in BMI. There was also a significant time \times smoking-status \times gender interaction, suggesting gender differences in the BMI change among ex-smokers but not among smokers. The relationship was such that female ex-smokers reported greater increases in BMI compared with their male counterparts. These analyses highlight the effects of gender on BMI increases among quitters.

Significance & future perspective

A strength of Munafò and colleagues' study is that it recognizes the confluence of previous basic and clinical findings that bear on the potential influences of the *OPRM1* genotype on NRT response. This includes: the complex interplay between the γ -aminobutyric acid, opioid and dopamine neurotransmitter systems in the psychoactive effects of nicotine [8,9]; the functional differences in opioidergic neurotransmission based on *OPRM1* genotype status [3,4], which has not been definitively characterized at this point; and a potential sexual dimorphism in the functionality of this allele [6]. The study by Munafò and colleagues reveals the various ways in which these variables interact in the NRT clinical trial, both in terms of short- and long-term clinical outcomes. Perhaps the clearest example of this is the three-way treatment-response finding, where the forms of *OPRM1* gene that were associated with long-term abstinence were actually opposite for males and females.

A recent example of the complex pharmacogenetic interactions involving the *OPRM1* gene that are emerging in the alcohol literature is the recent finding that, contrary to expectations, heavy drinkers with at least one *OPRM1* G allele who were taking naltrexone 50 mg actually reported increased craving for alcohol [10], whereas, in a more recent study, naltrexone was found to blunt alcohol-induced 'high' more strongly among carriers of the G allele [11]. Thus, in contrast to previous pharmacogenetic studies reporting high-magnitude interactions between single genetic loci and specific pharmacological agents that dramatically affect the medication's praxis [e.g., 12], Munafò and colleagues' study and other recent findings suggest that much more complicated relationships may exist. Indeed, for disorders with complex genetics, such as substance-use disorders, where substantial genetic influences appear to be conferred via small effects from an array of loci [e.g., 13], multifarious interactions may be more common than clear, high-magnitude pharmacogenetic relationships.

Importantly, Munafò and colleagues rightly sound several notes of caution with regard to these findings. One of the study's main findings is not consistent with a previous study by Lerman and colleagues and, although the two differ in some potentially important ways, they fundamentally reveal opposite pharmacogenetic effects, one favoring the possession of the G allele and the other favoring homozygosity for the A allele [7]. The history of genetic-association studies with regard to addictive behavior is replete with contrasting findings, with some studies reporting a significant association [e.g., 14] and others reporting null-findings [e.g., 15]; therefore, it is likely that this trend will be present to some extent in pharmacogenetic studies. The issue of consistency in the literature is an inherent challenge to the field of the behavioral genetics of addiction, where many potentially relevant genes exist but relatively few have been fully characterized in terms of their functionality. The design of mechanistic studies also does not permit examining more than one or two loci at a time or systematically examining gender effects [5,10]. As such, the need for subsequent replication to affirm the validity of an outcome will be essential for pharmacogenetic research in general, and to this study also.

In light of the fact that Munafò and colleagues' study was methodologically sound and generally well powered, these findings suggest the need for more intensive human laboratory research on the functional influence of polymorphisms of the *OPRM1* gene on both smoking (endo)phenotypes and response to NRT. To date, only one human laboratory study has been conducted in this area. Ray and colleagues found that female smokers who possessed at least one copy of the G allele selected regular cigarettes relative to placebo cigarettes significantly less often [6], reflecting the lower relative reinforcing value of nicotine. In addition, female smokers who were carriers of the G allele exhibited significantly less differentiation in their reports of satisfaction, liking and perceived cigarette strength between regular cigarettes and placebo cigarettes. No studies have examined *OPRM1* influences on differential responses to acute withdrawal or the relative alleviation of withdrawal by NRT, and gender effects have not been examined in either case. Furthermore, human laboratory studies will be necessary to directly test Munafò and colleagues' hypothesis that *OPRM1* may play a critical role in influencing gender differences in long-term smoking cessation outcomes by way of genetic effects on BMI.

In a broader sense, the field of pharmacogenetics is likely to make more rapid progress by focusing on genetic polymorphisms of known functional impact on drug metabolism, disposition, drug transporters or the target of a medication (e.g., a receptor or enzyme) [2]. In these cases, the effects of a medication are more closely linked to specific biological mechanisms, thereby strengthening the theoretical rationale for a potential association between a given genotype and a pharmacotherapy. Such a framework is critical for interpreting both significant and null pharmacogenetic findings and for translating those findings into clinical recommendations. Regarding theoretical rationale, for example, the *OPRM1* genotype examined by Munafò and colleagues has been tested in the context of responsiveness to naltrexone, an opioid antagonist thought to act selectively for μ -opioid receptors and used as a treatment for alcohol-use disorders [10,11,16]. In the case of naltrexone, the *OPRM1* genotype is of interest for its putative functional effects on μ -opioid receptors, which in turn are the primary target of this pharmacotherapy. Although the genotype in question is the same and the addictive behaviors have important similarities, the rationale is clearly different. A related theory-driven approach for translating behavioral genetics research into clinical practice has been proposed by focusing on craving for alcohol and tobacco as an important biobehavioral mechanism in addictions [17]. The issue of theoretical rationale is especially important in the context of candidate-gene studies, which must focus on a few theory-driven genetic variants at a time, as opposed to using high-throughput data-driven pharmacogenomic approaches [e.g., 18].

Finally, as demonstrated by Munafò and colleagues, pharmacogenetic studies are stronger to the extent that they integrate knowledge from basic and applied science. Specifically, knowledge regarding the functional significance of genotypes may allow us to make more precise predictions regarding the impact of those genetic variants on behavioral outcomes and the specific mechanisms by which genetic determinants may operate. This in turn may result in more targeted treatment algorithms. To that end, a combination of molecular studies focusing on the functional significance of genes, laboratory studies examining specific mechanisms of action and clinical trials focusing on the clinical value of putative genetic moderators of medication response will all be necessary in order to fulfill the promise of optimizing pharmacotherapies based on genetic variability.

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