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"Searching for Evidence of Genetic Mediation of Opioid Withdrawal by Opioid Receptor Gene Polymorphisms."

Recommendation: accept minor revisions

Background: this study explores the relationship between genetic polymorphisms and the severity of opioid withdrawal. The authors collected data from 48 daily heroin users who previously completed a standardized abstinence-induced or naloxone-precipitated withdrawal. The total withdrawal severity score was correlated with genotype information for variants of OPRM1 (rs1799971;rs6848893), OPRD1 (rs10753331; rs2234918; rs581111; rs678849; rs1042114) and OPRK1 (rs6473797; rs963549). Three polymorphisms were significantly associated with severity of abstinence-induced withdrawal in the bivariate analysis (R): OPRM1 rs6848893 (0.45), OPRD1 rs10753331 (0.03) and rs678849 (0.08), but only the OPRM1 rs6848893 was retained in the multivariate model (p <.001). For participants who underwent naloxone-precipitated withdrawal (n = 29) only OPRK1 rs6473797 (-0.23) was significant in the bivariate analysis, though not retained in the final model. The authors concluded that this data provide evidence for genetic modulation of opioid withdrawal severity, and suggest there may be qualitative differences between withdrawal resulting from abstinence and antagonist-precipitated withdrawal.

I commend the authors for the choice of this study as it has important clinical implications. I would like to suggest minor revisions to improve the quality of this manuscript further.

1. In the background section please provide some information on withdrawal and when you mention your hypotheses please introduce the concepts of abstinence induced and naloxone withdrawal. What has previous literature reported about these two states? Are they comparable? Did you expect to find differences when comparing the two states?
2. In the methods section please provide additional details on the clinical assessment of the participants such as psychiatric comorbidities, clinical scores on scales such as MADRAS or YMRS. Please provide means and SD of these clinical scores in table 2.
3. In the statistical section please provide additional details on the regression analysis. Did you use a hierarchical regression analysis? Using blocks of variables (e.g. demographic, clinical, genetic polymorphisms) could be a robust way of conducting this type of analyses. Did you check for normality across all variables? What was your threshold to determine statistical significance? (p=0.05 for example)
4. In table 3 when you provide the regression findings please provide R2s of your models.
5. In table 2 please make sure to provide t/F or chi-square values along with with p-values.