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## **Using human genetic studies of OUD to optimize the choice of mouse strains and assays for GWAS variant characterization and preclinical research**

Modeling complex human traits in animal models typically entails choosing assays with the best predictive, face, and construct validity. The opioid intravenous self-administration assay is a gold standard for volitional drug use in model organisms. The inbred C57BL/6J (B6) mouse strain has long been the dominant model in neuroscience research, adopted widely in the hope that strain standardization would ensure reproducibility across laboratories worldwide. As a result, much of our foundational understanding of addiction-like behavior in mice rests on findings generated in this single strain. There is a tremendous range of variation in self-administration, physiological effects of the drug, including opioid-induced respiratory depression, and other aspects of drug use and OUD. OUD susceptibility is influenced by variations across multiple biological pathways, each of which varies across strains of laboratory mice. We have developed 'Strain Recommender', a data-driven approach to optimize the choice of background strains based on resemblance to human genetic risk for disease. This tool prioritizes over 600 mouse inbred strains and virtual F1 hybrids based on their biological resemblance to the most vulnerable or resistant aspects of the disease state. Using data from the Million Veterans Program and other sources, on OUD and problematic prescription opioid misuse, presented in Sullivan et al. 2025, we identified mouse strains expected to be most sensitive (or resistant) to oxycodone self-administration. This approach to optimizing the mouse model that more closely resembles the disease state enables the design of genetic manipulation and pharmacological intervention studies with the greatest translational relevance.

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