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Prescription opioid use and risk for major depressive disorder: a multivariable Mendelian randomization analysis

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Growing evidence suggests prescription opioid use and other pain medications impact depression and anxiety disorders; however, observational studies are subject to confounding and reverse causality, making causal inference difficult.

We performed two-sample Mendelian randomization (MR) using summary statistics from recent genome-wide association studies (GWAS) to assess associations of self-reported prescription opioid (N=78,808) and non-opioid analgesics, including nonsteroidal anti-inflammatories (NSAIDs, N=164,520) and acetaminophen-like derivatives (N=112,010) use on MDD (N=143 265) and ASRD (N=31,890) to investigate potential bidirectional relationships between genetic liability for pain medication use and both major depressive disorder (MDD) and anxiety and stress-related disorders (ASRD).

In a combined sample of 737,473 study participants, single-variable MR showed genetic liability for increased prescription opioid use increased risk of both MDD (odds ratio per unit increase in log odds (OR) opioid use=1.14, 95%, CI 1.06-1.22, *P*<.001) and ASRD (OR=1.24, 95% CI 1.07-1.44, *P*=.004). Using multivariable MR, these opioid use estimates remained after accounting for non-opioid pain medications (MDD-OR=1.14, 95% CI 1.04-1.25, *P*=.005; ASRD-OR=1.30, 95% CI 1.08-1.46, *P*=.006). Bidirectional analyses showed genetic liability for MDD, but not ASRD, increased prescription opioid use risk (OR=1.18, 95% CI 1.08-1.30, *P*<.001). Estimates were generally consistent across inverse variance weighted (IVW) and MR-Egger sensitivity analyses. Pleiotropy-robust methods did not indicate bias in IVW estimates.

Our findings suggest evidence for potential causal relationships between genetic liability for increased prescription opioid use and risk for MDD and ASRD. These findings may inform prevention and intervention strategies directed towards the opioid epidemic and depression.