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Network medicine and electronic health record-based discovery of repurposable drugs for neonatal opioid withdrawal syndrome (NOWS)

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Background: Neonatal opioid withdrawal syndrome (NOWS) contributes to approximately 20 per 1,000 live births with hospitalization. While the incidence of NOWS is on an increasing trend in the United States (US), pharmacotherapeutic treatments for NOWS are either symptomatic and/or have controversial efficacy.

Rationale/Significance: The development of multi-omics data integration and electronic health records data facilitate the identification of clinically relevant repurposable drugs. If repurposable drugs could be identified for NOWS, the treatments could promote the health for children with NOWS.

Hypothesis: We hypothesize network medicine based drug screening from multiomics data (genetics/genomics from individuals with NOWS) and mining of health record data could identify repurposable treatments for NOWS.

Results: We established the drug-disease module using experimentally validated drugs/genes/proteins associated with NOWS derived from integrative analysis of genetic and genomic profiles. Combining in silico network medicine-based prediction and pharmacoinformatics screening of a large US health record data (N=0.89 million). We identified 6 candidate repurposable drugs for potential treatment of NOWS, including acetaminophen, guaifenesin, levothyroxine, azithromycin, ibuprofen, and metoclopramide. Further, we performed covariate-matched case-control study using mother-child dyad data. We identified maternal azithromycin exposure was associated with reduced risk of NOWS in all trimesters (odds ratios <0.67, P-values <0.0095). Further drug-target network analysis implies potential drug's mechanism-of-action linked to reduced risk of NOWS from real-world patient data.

Discussion: We demonstrated azithromycin is significantly associated with reduced risk of NOWS. Further clinical trials and experimental validations are warranted for revealing the clinical effect size and target engagement of azithromycin in treatment of NOWS.