

## **The Effect of Varenicline on Ethanol Consumption and Striatal Gene Expression Using Classical Analytical Tools and High-Dimensional Mediation Analysis**

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In recent years, varenicline has been shown to decrease ethanol consumption in adult rodents without effecting consumption of other sweet, rewarding solutions. Varenicline is a partial agonist at alpha4 beta2 nicotinic acetylcholine receptors, but has been shown to interact with other receptors at high concentrations. Importantly, removal of the alpha4 or beta2 nicotinic subunits does not completely reverse varenicline's effect on ethanol consumption. Thus, in order to gain a greater understanding of the mechanisms by which varenicline decreases ethanol consumption, we performed RNA sequencing on striatal tissue from animals treated with varenicline or saline prior to an ethanol binge session. Using classical tools to analyze RNA sequencing data, we found 810 differentially expressed genes using Cuffdiff and 1 significant co-expression network using WGCNA. However, these analyses are not able to account for both treatment and expression differences to explain behavioral outcomes in the same model. As a novel strategy, we employed a high-dimensional mediation analysis. In this analysis, we selected top genes that were related to both the treatment group and the behavioral outcome (alcohol consumption). This analysis yielded a number of candidate genes that were not identified with the classic tools, some of which have previously shown relationships with drug abuse measures. These results identify novel candidate genes that may underlie the effects of varenicline on ethanol consumption.