Hypothesis: Tobacco Use Disorder (TUD) disproportionately affects psychiatric patients in general and, for patients with Bipolar Disorder (BD), the risk for TUD is almost 3 times that for the general population based on our meta-analysis consistent with some common underlying etiology. Both BD and TUD show strong evidence of genetic influences on susceptibility. Given evidence of common etiology and evidence of genetic influences, we hypothesized common genetic influences on the etiology of BD and TUD.

Risk for Tobacco Use Disorder (TUD) among Bipolar Disorder (BD) patients is almost three times that of the general population. Using the MIX program, we conducted a meta-analysis of the seven studies that have been published on risk for comorbid BD with TUD. Relative risk is estimated at 2.77, significant at p-value < 0.01, and 95% confidence interval 2.62 to 2.92, with smoking modeled as a fixed effect and Mantel-Haenszel weighting.

Network hypothesis testing: We tested each of these networks for association with BD and TUD using the Genetic Association Database (GAD), available through the DAVID interface at NIAID. We submitted the list of genes from each network and DAVID returned a table of GAD terms with the genes tagged for each annotation, p-value and FDR for over-representation of genes tagged with each term, and fold enrichment. For each network, we did the hypothesis testing both including the validated candidates and excluding them. Only the GeneGo network was significantly enriched (FDR < 5%) for both BD and TUD when we excluded the validated candidates.

Candidate SNPs: Based on the statistically significant association of the GeneGo network with both BD and TUD, we hypothesize that any of the genes in this network could impact susceptibility for the comorbidity. To date, no Genome Wide Association (GWA) studies have been conducted for comorbid BD with TUD. However, we used three lines of evidence to prioritize SNPs for follow on study. We combined evidence from the NicSNP GWA study for nicotine addiction, the GAIN GWA study for BD with TUD, and functional data based on the GIN algorithm. We weighted each SNP by the sum of –log(p-value) in each of the GWA studies, plus weights for % evolutionary conservation with mouse and SNP function (i.e. non-synonymous substitution, missense substitution). We tested each of these networks for association with BD and TUD using the Genetic Association Database (GAD), available through the DAVID interface at NIAID. We submitted the list of genes from each network and DAVID returned a table of GAD terms with the genes tagged for each annotation, p-value and FDR for over-representation of genes tagged with each term, and fold enrichment. For each network, we did the hypothesis testing both including the validated candidates and excluding them. Only the GeneGo network was significantly enriched (FDR < 5%) for both BD and TUD when we excluded the validated candidates.

Summary and Conclusions: Based on our meta-analysis, we find strong evidence of bidirectional relative risk for BD and TUD, suggesting some common etiology for these disorders. Both disorders show evidence of genetic influences on susceptibility, consistent with a common genetic etiology. Gene2MeSH nominates COMT, DAT, and SERT as candidate genes for the comorbidity and we find strong evidence to support their roles. PDG-ACE identifies significant commonality among these genes consistent with psychiatric disorders, substance use disorders, attention deficit disorder, and gender specific effects in these disorders. No gene functions alone, so we used three algorithms to hypothesize gene networks consistent with roles that our candidate genes might play in the comorbidity. Based on hypothesis testing via the GAD, we find that the GeneGo network is significantly associated with both disorders, even when the established candidate genes are not included. All of the genes in this network are candidates for influencing the comorbidity and we have produced a set of prioritized SNPs for follow-on testing.

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