The harmful influence of social disconnection on risk of substance misuse is well-researched. However, our study is the first to analyze the interactive effects of isolation and loneliness with the reinforcement models of addiction to assess risk of problematic alcohol and drug use under the COVID-19 pandemic. A sample of young adults (N=144, 58% white, 25% African American, 6% Hispanic) completed a questionnaire evaluating frequency of substance-use related problems, frequency of virtual and face-to-face interaction, motivations for substance use as positive or negative reinforcement, and perceived loneliness. Results indicated that physical, but not virtual, isolation is associated with loneliness; additionally, though women experience more loneliness at low levels of physical isolation, only higher levels of physical isolation were associated with greater loneliness in men. The interaction of loneliness with positive reinforcement motives was associated with greater risk of substance use problems, but similar interaction models of loneliness with either negative reinforcement motives or gender were insignificant, as was the interaction of physical isolation with either reinforcement motives or gender. Lastly, men reported more positive reinforcement motives for drug use, but no gender differences in negative reinforcement motives were found. Future studies should incorporate larger and more diverse samples and should investigate the interaction of isolation and loneliness with other substance use risk factors.