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Young Investigator Award Symposium

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Abstract

This article highlights the research presented at the inaugural meeting of *Alcoholism and Stress: A Framework for future Treatment Strategies.* This meeting was held on May 6–8, 2008 in Volterra, Italy. It is an international meeting dedicated to developing preventive strategies and pharmacotherapeutic remedies for stress- and alcohol-related disorders. For the first time, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) conferred a Young Investigator Award to promote the work of young researchers and highlight their outstanding achievements in the fields of addiction medicine and stress disorders. The awardees were Dr. Katie Witkiewitz (University of Washington), Dr. Andrew Holmes (NIAAA), Dr. Lara A. Ray (Brown University), Dr. James Murphy (University of Memphis), and Dr. Heather Richardson (The Scripps Research Institute). The symposium was chaired by Drs. Fulton Crews and Antonio Noronha.

Keywords: Alcohol; Stress; Human; Mouse; Rat; Glutamate; Naltrexone; HPA axis

Introduction

Alcoholism and Stress: A Framework for Future Treatment Strategies is an international meeting dedicated to developing preventive strategies and pharmacotherapeutic remedies for stress- and alcohol-related disorders. To promote the work of young researchers and highlight their outstanding achievements in the fields of addiction medicine and stress disorders, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) conferred a Young Investigator Award at the inaugural meeting in Volterra, Italy.

This is the first **Young Investigator Award** to be sponsored and funded by the **NIAAA (AA017581)**. This award is intended to facilitate innovative research opportunities and support alcohol researchers. Applications were received from scientists throughout the United States and Europe. Applications were reviewed by the conference organizers, Drs. Marisa Roberto and George Koob of The Scripps Research Institute (La Jolla, CA). The main criteria for selecting awardees were as follows: (1) scientific merit of the submitted abstract, (2) previous publication record, (3) present work in the alcohol research field, and (4) potential for development and contribution to alcohol and stress research. Those judged to be outstanding in quality were selected to be recipients of the Young Investigator Award.

Five Young Investigator Award recipients were selected and invited to give a presentation during the Young Investigator Symposium, chaired by Dr. Fulton Crews (University of North Carolina at Chapel Hill) and Dr. Antonio Noronha (NIH/NIAAA). Awardees also received a waiver of the meeting registration fee and an official certificate of merit from the meeting organizers.

Dr. Katie Witkiewitz (University of Washington) provided an overview of advanced statistical methods to study the correlation between stress and alcohol use across time. Dr. Andrew Holmes (NIAAA) showed data supporting

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the efficacy of novel antiglutamatergic and antidopaminergic drugs in the treatment of alcoholism. Dr. Lara Ray (Brown University) discussed the relationship between the clinical and diagnostic correlates of posttraumatic stress disorder (PTSD) and subsequent development of an alcohol use disorder (AUD). She also provided evidence for naltrexone (NTX) treatment for alcoholism. Dr. James Murphy (University of Memphis) presented data indicating that trauma, stress, and other psychiatric symptoms confer a high risk for alcohol-related problems in college students. Dr. Heather Richardson (The Scripps Research Institute) provided evidence of an imbalance of the hypothalamic and extrahypothalamic corticotropin-releasing factor (CRF) systems associated with alcohol dependence.

Examining the relationship between stress and alcohol use across time: recent advances in longitudinal data analyses

Katie Witkiewitz, Ph.D.

For over 30 years alcohol researchers have recognized the existence of multiple pathways in the relapse process. Yet, the statistical techniques used in the analysis of treatment outcome data have often failed to capture the individual variability in patterns of resumption after an initial lapse. Variation in drinking patterns is best demonstrated by examining individual differences in post-treatment drinking trajectories. There is tremendous variability both within and between individuals over time.

Fortunately, statistical techniques have been developed that can differentiate unique patterns in drinking and the risk factors that reliably predict these patterns. Two methods that have been increasingly used over the past few years in the alcohol and substance use literature, latent growth curve (LGC) models and growth mixture models (GMM; also latent class growth analysis), will be the focus of the present article. However, numerous other extensions of latent variable models are available (see Collins and Sayer, 2001; Hedeker and Gibbons, 2006; Rose et al., 2000; Singer and Willett, 2003).

Latent variable models, in general, assume that the relationship among observed measures can be explained by an underlying unobserved ''latent'' variable. In the case of LGC, the latent variables explain the repeated measurement of some observed variable, where the observed growth trajectory over time is modeled by a combination of fixed and random effects. Fixed-effects components are the mean values of the estimated trajectories and the random-effects components represent the variances around the mean trajectory. Growth mixture modeling (GMM) combines finite mixture modeling with LGC modeling by estimating a categorical latent variable that represents unobserved subpopulations of individuals with similar growth trajectories (Muthén, 2001; Muthén and Shedden, 1999). GMM enables the researcher to identify discrete typologies of mean growth trajectories in the population and individual heterogeneity within each trajectory type (using continuous latent variables).

The present study provides an example of using LGC and GMM to examine variation in weekly perceived stress scale scores (Cohen et al., 1983) during treatment in the Combined Pharmacotherapies and Behavioral Intervention (COMBINE) study (COMBINE Study Group, 2003) as a predictor of percent drinking days during treatment through 68-weeks after treatment. A LGC model with linear and quadratic effects provided a good fit to weekly stress data (comparative fit index [CFI] = 0.97; root mean square error of approximation [RMSEA] = 0.03), which demonstrated a decreasing trend in stress scores over the course of 12 weeks (linear slope = −0.33, $P < .005$). Treatment significantly predicted linear slope (B = 0.15 [SE = 0.04], $P < .005$), indicating that individuals who received the combined behavioral intervention (CBI) reported a greater decrease in stress over time, as compared with those who received medication management.

For the GMM analyses, a three-class model of drinking frequency (lapsers [8.6%], frequent drinkers [12.3%], and infrequent drinkers [79%]) provided the best fit to the observed data. Individuals with an increasing stress slope were 2.8 times more likely to be classified as lapsers and 3.2 times more likely to be classified as frequent drinkers, compared with infrequent drinkers. Receiving CBI was also related to drinking class membership, with lapsers having a lower odds of receiving CBI (odds ratio [OR] = 0.47, $P = .003$), as compared with infrequent drinkers; and frequent drinkers having a lower odds of receiving CBI (OR = 0.70, $P = .04$), as compared with lapsers. The results from this study suggest that assessing changes in stress during treatment could help identify individuals who are more or less likely to lapse after treatment. In addition, CBI was related to significant reductions in stress during treatment and less frequent drinking after treatment, compared with medication management.

Effects of antiglutamatergic drugs on sensitivity to ethanol's acute intoxicating effects in mice

Yi-Chyan Chen, M.D., and Andrew Holmes, Ph.D.

There is a growing evidence that the glutamate system plays a major role in the neural and behavioral actions of alcohol and the processes driving the development of alcoholism (Heilig and Egli, 2006; Spanagel and Kiefer, 2008). In rodents, pharmacological or genetic blockade of glutamate receptors alters the behavioral effects of ethanol (Boyce-Rustay and Holmes, 2005, 2006; Gass and Olive, 2008). This has led to growing interest in the potential efficacy of various clinically available drugs with ''antiglutamatergic'' properties for the treatment of alcoholism (Krupitsky et al., 2007). For example, six compounds (memantine, dextromethorphan, haloperidol, lamotrigine, oxcarbazepine, topiramate) with antiglutamatergic properties that are currently in clinical use for various indications (e.g., Alzheimer's disease,