

NIAAA-EAB Recommendations: Stress and Relapse

EAB mtg. of June 9-10, 2009

1. Characterize the phenomenology of the course of alcohol dependence, maintenance, abstinence and stress, as related to the dynamics of relapse and stress-related relapse.

- Resolve critical issues of time-course of dependence development, abstinence and relapse, with consideration of the transient vs progressive vs persistent effects of stress and alcohol exposure on relapse
- Explore the use of animal studies for modeling critical components of relapse and stress/relapse interactions
- Understand the relationship between dependence severity and stress-induced relapse (in both treatment and community samples)
- Distinguish factors that cause relapse -- e.g. stress, anxiety, negative affect etc.
- Investigate the cumulative effects of adversity/chronic stress (history and type of stress) on relapse propensity, including consideration of:
 - Developmental timing of stressor exposure (prenatal, adolescence and aging)
 - Critical periods
 - Gene/development interactions
 - Models of stress: Traumatic stress leading to altered acute responses to stressors and sometimes PTSD; HIV, high-crime, poverty as stressors

2. Use multifactorial measures in animal models to study processes contributing to stress-induced relapse across the lifespan:

- Investigate models of "relapse"-increased responding to cue and/or changes in drinking patterns
- Determine endophenotypes and intermediate adaptations associated with stress and relapse that can be examined in humans and animals (e.g., imaging, PPI, withdrawal, anxiety, sleep, fear conditioning, PTSD models)
- Assess the role of genetics in animal models of stress-induced relapse
- Focus on behavioral processes, including teasing out contributions of explicit and implicit learning, consideration of the role of response inhibition and alcohol seeking, and development of translational models of behavioral indices of stress-related relapse
- Consider the impact of developmental exposure to stressors and chronic repeated stressors on later drinking
- Examine interoceptive cues (heart rate, respiration and other autonomic responses) that are highly sensitive to learning history, associated with alcohol and stress, and that may serve as cues to trigger relapse
- Explore neuroimaging in animal models as a possible means to promote translational studies

3. Utilize multifactorial human models to study stress-induced relapse across the lifespan, including examination of:
- Stress-related comorbidities (e.g., mood, anxiety and other substance abuse)
 - Interoceptive cues (heart rate, respiration and other autonomic responses) that are highly sensitive to learning history, associated with alcohol and stress, and that may serve as cues to trigger relapse
 - Resilience mechanisms, pathways leading to positive and negative outcomes, and how behavioral & biological measures return to normal vs permanent changes
 - Groups of individuals at high vs low risk of relapse:
 - How much of the variance in comparisons across risk groups can be explained by biologic vs environmental factors?
 - What differs between alcoholics who have bottomed out (reached the criminal justice system because of alcohol abuse) and become/maintain abstinence vs those who relapse? Presumably they experience similar stresses, but differ in the magnitude of their stress response and the effect of stress on relapse.
 - What metabolomic, genomic, brain circuitry, immune and endocrine factors serve to protect abstinent individuals or contribute to vulnerability in individuals that relapse?
 - What do secondary analyses of data of high risk and low risk populations in such as the NESARC reveal about characteristics that differentiate individuals who quit on their own (natural recovery) vs those who continue to drink?

4. Characterize the interaction between stressors and alcohol on biological processes, including:

- structural (dendritic spines, circuitry)
- chemical (transmitter, immune, neuromodulators, neurosteroids)
- neural/glia
- genetic (e.g., gene expression/function 'epigenetics', histone and DNA modification, non-coding RNAs, etc) measures

Of particular interest is the overlay of stress/EtOH brain regions and circuitry (e.g. better understanding of prefrontal cortical-limbic interactions).

5. Identify stress-related markers predictive of relapse. Factors considered should include both peripheral and central markers in males and females, and in humans and animal models, with an emphasis on the determination of predictability (human studies) and causality (animal studies). Of particular interest are:

- Endophenotypes and intermediate adaptations that could be measured in animals and humans through indices such as:
 - PPI (Pre-pulse inhibition)
 - Behavioral measures (including anxiety and depression)
 - Sleep

- Measures of withdrawal (severity, number, course, type, etc)
- Endocrine, autonomic, neuroimmune measures
- Anxiolytic response to alcohol
- Markers that predict relapse and stress-induced relapse:
 - Genetic
 - Epigenetic
 - Molecular/cellular/proteomic
 - Neural circuits
 - Stress-related physiology (autonomic and HPA)
 - Pharmacological, cognitive, and behavioral
 - Social and cultural; sex, ethnicity

6. Characterize the spectrum of reversible biological responses to mild stress and pathological (irreversible) responses to severe and prolonged stress and how they relate to alcohol dependence. Include the spectrum of reversible low-dose ethanol effects on brain signaling events and circuits as well as the toxic effects of ethanol on some of the same signaling events and neural circuits.

7. Develop medications for relapse prevention.

- Explore potential pharmacotherapies for co-morbid disorders and stress (e.g., anxiety, depression, PTSD) as potential drugs to treat stress-induced relapse
- Integrate genetic/epigenetic/behavioral/neuroimmune responses to define new therapeutic targets and patient subgroups
- Develop medications to enhance behavioral therapies directed at relapse prevention