Published in final edited form as:

Alcohol Clin Exp Res. 2015 April ; 39(4): 587–588. doi:10.1111/acer.12664.

Commentary on Litten et al. (2014): Heterogeneity of Alcohol Use Disorder: Understanding Mechanisms to Advance Personalized Treatment

Howard C. Becker, Ph.D.

Charleston Alcohol Research Center, Departments of Psychiatry and Neuroscience, Medical University of South Carolina & Department of Veterans Affairs Medical Center, Charleston, SC 29425

Tailoring treatment to individuals that present with distinct aspects of AUD, which is heterogeneous, is a desirable goal, but it will require a better definition of AUD subtypes and their unique underpinnings than are currently available. Litten et al. describe a framework within which to organize scientific inquiries and discoveries into distinct AUD domains of core dysfunctions, each defined by a series of constructs with unique underlying mechanisms. This schema is fashioned after the Research Domain Criteria (RDoC) recently adopted by NIMH (Cuthbert, 2014; Insel et al., 2010).

There are a number of appealing aspects of this approach that are relevant to the alcohol field. First, this model promotes research that focuses on measurable outcomes related to specific characteristics and subtypes (sub-phenotypes) of AUD rather than simply targeting broadly defined diagnostic criteria. Second, this approach provides a framework for more refined clinical investigations that can take into account specific characteristics of AUD. Currently, recruitment is usually limited to either treatment-seekers or non-treatment-seekers. Third, the model provides a framework to study complex constructs integral to addiction through the coordinated use of animal models and human laboratory investigations at several levels of analysis, spanning molecular and genetic factors, cellular processes, and neural circuitry and systems approaches. Finally, this schema encourages integrative, multi-disciplinary strategies to elucidate underlying mechanisms, enabling a more comprehensive analysis of AUD constructs that are essential to advance therapeutics.

Despite solid empirical evidence to support this proposed framework, caution should be exercised in compartmentalizing areas of dysfunction within the purported three stages of addiction. While convenient to devise cross-sectional matrices for these three stages, it is important to recognize the progressive nature of alcoholism, which is likely to involve changes in all functional areas across all stages. Thus, research will need to focus not only on mechanisms underlying constructs within a specific domain, but also how such mechanisms relate to changes in the same construct or similar ones for other AUD domains of study.

Finally, with the growing interest in personalized medicine, the role of genetics in influencing treatment outcome for AUD has received increasing attention (Kranzler and McKay, 2012). Indeed, as noted by Litten et al., several studies have shown genotype to play an important role in governing treatment outcome. This has been demonstrated for the mu opioid receptor antagonist naltrexone (Schacht et al., 2013), the serotonin-3 receptor antagonist ondansetron (Johnson et al., 2013), and the anticonvulsant topiramate (Kranzler et al., 2014). However, these findings are not entirely consistent (e.g., Garbutt et al., 2014) and there is a need for prospective study designs to confirm the role of these genetic variants in moderating pharmacological treatment outcomes. Also, this is an area where coordinated clinical and preclinical efforts may be especially fruitful. As genetic analyses of human subpopulations with AUD reveal unique polymorphisms of interest, use of genetically engineered animals can be used to directly test hypotheses about their relevance to the disease itself as well as their role in moderating treatment efficacy. Some examples of this strategy already exist (e.g., Bilbao et al., 2014; Ramchandani et al., 2011) and this is an area of research that is likely to grow as the search for genetic moderators of treatment outcome continues to gain momentum in the field.

Acknowledgments

This work was supported by NIAAA grants P50 AA010761 and HHSN275201400004C, and VA Medical Research. The author thanks Dr. J. Schacht for his helpful comments on this manuscript.

References

- Bilbao A, Robinson JE, Heilig M, Malanga CJ, Spanagel R, Sommer WH, Thorsell A. Biol Psychiatry. 2014 Epub ahead of print.
- Cuthbert BN. The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. World Psychiatry. 2014; 13:28–35. [PubMed: 24497240]
- Garbutt JC, Greenblatt AM, West SL, Morgan LC, Kampov-Polevoy A, Jordan HS, Bobashev GV. Clinical and biological moderators of response to naltrexone in alcohol dependence: a systematic review of the evidence. Addiction. 2014; 109:1274–1284. [PubMed: 24661324]
- Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P. Research Domain Criteria (RDoC): Toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010; 167:748–751. [PubMed: 20595427]
- Johnson BA, Seneviratne C, Wang XQ, Ait-Daoud N, Li MD. Determination of genotype combinations that can predict the outcome of alcohol dependence using the 5-HT(3) antagonist ondansetron. Am J Psychiatry. 2013; 170:1020–1031. [PubMed: 23897038]
- Kranzler HR, Covault J, Feinn R, Armeli S, Tennen H, Arias AJ, Gelernter J, Pond T, Oncken C, Kampman KM. Topiramate treatment for heavy drinkers: moderation by a GRIK1 polymorphism. Am J Psychiatry. 2014; 171:445–452. [PubMed: 24525690]
- Kranzler HR, McKay JR. Personalized treatment of alcohol dependence. Curr Psychiat Rep. 2012; 14:486–493.
- Ramchandani VA, Umhau J, Pavon FJ, Ruiz-Velasco V, Margas W, Sun H, Damadzic R, Eskay R, Schoor M, Thorsell A, Schwandt ML, Sommer WH, George DT, Parsons LH, Herscovitch P, Hommer D, Heilig M. Mol Psychiatry. 2011; 16:809–817. [PubMed: 20479755]
- Schacht JP, Anton RF, Voronin KE, Randall PK, Li X, Henderson S, Myrick H. Interacting effects of naltrexone and OPRM1 and DAT1 variation on neural response to alcohol cues. Neuropsychopharmacology. 38:414–422. [PubMed: 23032071]