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Letter to Editor in Response to Johnson's Commentary (2017) on the Witkiewitz et al. (2017) Article

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Dr. Bankole Johnson's commentary (Johnson, 2017) on the recent article by Witkiewitz et al. (2017) was a thoughtful piece, emphasizing several important points that should be considered when developing evidence-based regulatory guidelines for conducting alcohol treatment trials. In particular, Dr. Johnson reiterated the importance of 1) having the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) endorse comparable primary endpoints, 2) developing an endpoint that accurately reflects a reduction in the behavioral and medical risk levels of drinking, and 3) defining more sensitive clinical trial endpoints to detect differences between the experimental medication and placebo groups. The latter point is particularly important because medications showing efficacy in alcohol treatment trials generally have small effect sizes (Falk et al., 2010; Litten et al, 1996 and 2005; Zindel and Kranzler, 2014).

Drinking endpoints remain the most sensitive measure for assessing the efficacy of treatment, especially when compared with non-drinking endpoints, like craving, alcohol-related consequences, and measures of mental health (Litten et al., 2013). The FDA has

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approved two primary dichotomous measures as successful clinical trial outcomes: “total abstinence” and/or “no heavy drinking days.” Each of these primary outcomes must be clinically relevant; that is, there needs to be improvement in how patients feel and function, both to meet the endpoint criterion for these outcomes and to achieve acceptable FDA regulatory value (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm433618.pdf).

The paper by Witkiewitz et al. (2017) explores another potential drinking endpoint: change in the World Health Organization (WHO) risk levels of alcohol consumption (very high risk, high risk, moderate risk, and low risk) during an alcohol treatment trial. The validity and practicability of that endpoint is being investigated by the Alcohol Clinical Trials Initiative (ACTIVE) Group, which brought together representatives from the pharmaceutical industry, FDA, EMA, academia, the National Institute on Alcohol Abuse and Alcoholism, and the National Institute on Drug Abuse, in an effort to improve the methodology of alcohol clinical trials (Anton et al., 2012). Johnson (2017) refers to this endpoint as a hydrid/composite model, combining measures of alcohol consumption and its health consequences. This is a subtle point that we believe needs clarification. WHO risk levels are simply categories of alcohol consumption and do not include health consequences, an important distinction for readers to appreciate in interpreting our work and intent. To reiterate,Witkiewitz et al. (2017) did show (through secondary analysis of the COMBINE data set) that reductions in the WHO risk drinking levels during treatment were associated with significantly fewer alcohol-related consequences and improved mental health. This is an important first step in meeting the FDA’s criteria for an acceptable primary endpoint: it validates the potential of the WHO endpoints by demonstrating that patients, by and large, feel and function better when WHO risk drinking levels are reduced.

The ACTIVE group is continuing to examine the WHO risk drinking levels. Another validation study is drawing on data from the longitudinal U.S. National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) to determine if reductions in the WHO risk drinking levels are associated with reductions in the prevalence of alcohol dependence in the general population. A second effort directly addresses Dr. Johnson’s concern that changes in WHO risk drinking levels may not be precise enough to detect the subtle medication differences found in a randomized controlled clinical trial. Using data from several well conducted and published multisite alcohol treatment trials (including the COMBINE Study), our group is currently examining whether the WHO endpoint adequately detects differences between experimental medication and placebo groups.

The EMA already agreed to a category shift in the WHO risk levels of drinking as a secondary endpoint in European alcohol pharmacotherapy trials (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500074898.pdf). The new evidence showing the clinical relevance of changes in the WHO risk levels of drinking may lead the EMA to include this as one of their primary endpoints. Likewise, with increased evidence to support this measure, the FDA also may consider it as a primary endpoint. Then, as Johnson (2017) highlighted in his commentary, change in WHO risk levels would serve as a common primary outcome measure for both the FDA and EMA, benefiting researchers and

pharmaceutical companies in their efforts to develop novel alcohol treatment medications and to foster their adoption by clinicians in real-world settings.

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