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Subjective Responses to Alcohol: A Paradigm Shift May Be Brewing

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Background: The meta-analysis by Quinn and Fromme (2011) is reviewed and integrated into the larger field. Guidelines for future research are presented.

Results: With results of the meta-analysis along with those of a recent comprehensive prospective study by our group (King et al., 2011), there is a call to the field to specify terms and integrate theoretical frameworks to advance our knowledge and improve comparisons across trials.

Conclusions: The meta-analysis is both timely and thorough and will provide clinical researchers with important information to move the field forward.

Key Words: Alcohol, Meta-Analysis, Alcohol Effects, Biphasic Alcohol Effects, Subjective Response, Risk for Alcoholism.

QUINN AND FROMME'S (2011) meta-analysis article represents an important, systematic, and timely quantitative investigation of over 30 years of research on subjective alcohol response in young alcohol drinkers to better understand risk factors for the development of alcohol dependence. The authors should be highly commended for their efforts in this worthwhile article that will most likely have a large impact on the field. The article is appropriately inclusive of studies examining persons at heightened risk for alcohol dependence by virtue of the longstanding definition of positive biological (often paternal) family history of an alcohol use disorder and the more recently elaborated heavy social drinking phenotype, that is, individuals who engage in frequent binge drinking (5 or more drinks per occasion for men, 4 for women; Substance Abuse and Mental Health Services Administration, 2006). It has been nearly 20 years since a critical, large-scale quantitative analysis has been undertaken (Pollack, 1992). As pointed out in several recent publications (Morean and Corbin, 2010; Newlin and Renton, 2010), over the past 2 decades, much important work has been untaken to elucidate and expand our understanding of the myriad of responses to alcohol and how they may relate to alcohol problems and consequences over time. In this commentary, our goal is to summarize the importance of Quinn and Fromme's analysis and to incorporate findings from our recent comprehensive alcohol challenge study (King et al., 2011), which was not published in time to be included in the meta-analysis. We also provide guideposts to sharpen future subjective response research to include necessary descriptive information of measures and constructs and to advance science to include rapidly developing translational, genetic, and neurobiological tools that will become increasingly important in the coming decades.

The meta-analysis article of Quinn and Fromme included systematic methods for identifying relevant peer-reviewed publications on human laboratory-based alcohol research through October 2010 that initially yielded over 500 articles. After appropriate selection criteria, the number of articles was pared down significantly to 29 articles with over 1,300 participants. Briefly, the findings indicated that persons with positive (vs. negative) family history experienced reduced subjective response to alcohol, particularly among men, and that heavy drinkers (vs. lighter) experienced more stimulant and less sedative alcohol effects. The authors concluded that both low-level response (Schuckit, 1980) and differentiator models (Newlin and Thomson, 1990) were supported and in fact, the models may be describing 2 distinct phenotypic risk factors for future alcohol dependence.

While this analysis represents an important bridge for future research and the authors accomplished a Herculean task in putting together such complex analyses, there are a few points worth mentioning to guide interpretations of the findings. First, it is notable that measurements and scales varied as a function of risk group studied with primarily sedative measures used in studies of family history and measures of biphasic stimulant and sedative effects used in studies of drinking phenotype. It is curious why more convergence of measures has not been undertaken. In addition, some studies used a single visual analog item for the term "intoxication," but this may be problematic as this term may have bimodal (positive or negative) interpretations among participants and is likely insufficient to measure the complexity and myriad of alcohol response (Martin et al., 1993). Second, and more

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Commentary on Quinn and Fromme (2011).

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importantly, analyses combining all subjective effects on each blood alcohol concentration (BAC) curve limb (see Table 3 in Quinn and Fromme) may not be as informative as the authors intended, as positively valenced stimulant responses during the rising limb were included with the more negative-valenced sedative responses when calculating effect sizes. Combining such responses may be like combining apples and oranges; the lack of significant effects observed for limb-specific analyses could be due to opposing responses canceling each other out. Similarly, examination of a measure across the entire postdrinking interval may also be problematic, as alcohol produces biphasic and dynamic temporal effects on many domains. As an example, a summation of stimulation scores throughout the entire postdrinking interval may produce a zero net sum for those with increases during the early BAC phase but decreases during the latter phase (see King et al., 2011). Some of these difficulties may be inherent in the lack of specificity of the theories themselves, as well as the analytic challenges with lack of independence of effect sizes faced by Quinn and Fromme. Ultimately, the last set of analyses (see Table 4 in Quinn and Fromme) specified effect sizes by measurement type and phase, and provided tests of critical components of the models.

While the meta-analysis summarizes important and critical studies through October 2010, the field is rapidly developing and further advances have been made in the year since the analyses that are deemed worthy of mention and integration. We recently published (King et al., 2011) a large and comprehensive dose-ranging human laboratory and prospective study examining positive-like alcohol responses, including stimulation, liking, and wanting, as well as sedative-like responses in a sample of 190 heavy and light social drinkers, which is larger than any study assessed in the meta-analysis. We minimized expectancy by not specifying it was an alcohol study (Conrad MF, McNamara PJ, & King AC, unpublished data), included specific alcohol response domains at various postdrinking phases, and conducted frequent monitoring of drinking behaviors, diagnoses, and consequences for 2 years after the laboratory sessions. Results of our study were consistent with those in the meta-analysis and showed that heavy drinkers, compared to light drinkers, exhibited significantly greater stimulating and rewarding subjective effects (liking and wanting), particularly during rising to peak breath alcohol concentrations (BrACs), and lower sedative and cortisol responses, particularly during declining BrACs (King et al., 2011). The Hedge's g effect sizes for stimulation during the ascending limb and sedation during the descending limb were 0.040 and −0.54, respectively (unpublished data), similar to what Quinn and Fromme found in their meta-analyses of biphasic effects by drinking history.

Not included in the meta-analysis were analyses investigating the predictive relationship between alcohol response and future drinking, which is likely a function of the paucity of longitudinal studies. In our study (King et al., 2011), follow-up assessments over 2 years revealed that among heavy drinkers, 4 trajectory groups emerged over time, including those who exacerbated binge drinking frequency, those who remained at high or moderate frequency binge drinking, and those who matured out of binge drinking. Only 2 subgroups emerged for light drinkers, both with predominantly light drinking patterns and rare binge drinking behaviors. Among heavy drinkers, our findings replicated those of Schuckit and Smith (1996) in that lower level response to alcohol's sedative effects predicted future alcohol drinking over time. At the same time, we found that greater alcohol response in terms of positive-like effects (stimulation, liking, wanting) also predicted future drinking. Further, while only two-thirds of the sample could be classified on family history, those with a positive or negative family history did not differ on alcohol responses, and controlling for family history in the main analyses also did not alter the main findings. We concluded that both the widely held low-level response theory and differentiator model should be revised to a degree. At least among heavy social drinkers, stimulant and rewarding alcohol responses, even at peak BrAC appeared to be important predictors of future alcohol problems, thus a modified differentiator model was proposed.

In Quinn and Fromme, the authors conclude that their meta-analysis provides some support for both low-level and differentiator models and that family history and drinking phenotype may be separate risk factors for the development of alcoholism. Although few studies have examined both risk factors in the same sample, research from our group provides some support for the possibility that positive family history and heavy drinking behaviors may be independent risk factors given the lack of additive or interactive effects on psychomotor tasks (Brumback et al., 2007), eye tracking responses (Roche and King, 2010), and subjective effects (King et al., 2011). While empirical evidence suggests that these risk factors may be separate, it is unclear theoretically and physiologically how they would exist independently of each other. For example, if those with a positive family history possess an inherent low-level response to alcohol, their heightened risk for alcoholism is hypothesized via a need to drink more alcohol to obtain the effect desired, and if these responses continue over time, they would naturally lead to increased drinking and alcohol use disorder diagnoses. Interestingly, as Quinn and Fromme point out, and to our knowledge, there has not been a specific test of the hypothesis that low-level responders have higher drinking levels at some critical point in time that precedes or leads to alcohol use diagnoses. If such persons have a low-level of sedative response to alcohol, it is unclear if they would be at risk to eventually feel sluggish alcohol effects if they continue consuming more alcohol during such episodes. Furthermore, as elucidated by Morean and Corbin (2010), continuing to drink despite feeling reduced positive effects of alcohol counteracts conventional notions of motivated behavior.

In putting perspective on subjective alcohol response research for the future, we would be remiss if we failed to include the potential importance of neurobiological, genetic, and translational animal models. Recent functional magnetic

resonance imaging research has progressed in examining alcohol effects on cue reactivity in heavy drinkers (e.g., Filbey et al., 2008) and on working memory in low responders (Trim et al., 2010), and there is great potential for newly evolving imaging technologies to help elucidate the neurobiological substrates of positive hedonic and sedative effects underlying responses to various doses of alcohol. Advances in neuroimaging and analysis techniques (Calhoun et al., 2009; Meyerhoff and Durazzo, 2008) may enable close examination of the specific brain regions, neurotransmitters, and functional circuitry underlying differential alcohol responses across the BAC curve. In a similar vein, molecular technology advances will enable a greater understanding of genetic factors associated with acute alcohol responses. While research using the candidate gene approach has yielded many promising results, it has also limited the focus to a small number of genes. Potential alternatives are genome-wide association and linkage analyses (Ducci and Goldman, 2008), which will require both larger sample sizes than used in past acute administration studies and identification of robust and distinct subjective response endophenotypes. Finally, translation of human paradigms to animal models will also be crucial, as animal models hold the ability to control and manipulate genetic factors and allow examination of acute alcohol responses during initial exposures that precede heavy consumption patterns (Crabbe et al., 2010). Despite this promise, ideal translational animal phenotypes that relate to human subjective responses still need to be identified (Crabbe, 2010).

In closing, we would like to put forth a call to further develop the growing paradigm shift in the field to move forward effectively and communicate findings to advance our understanding of the complexities of the role of alcohol responses to vulnerability to alcohol problems and diagnoses. First and foremost, we suggest that future researchers cease use of general and nonspecific terminology such as "level of response to alcohol" or "alcohol sensitivity" without specifying 4 important factors: (i) the response being measured, (ii) the amount and rate of alcohol administered, (iii) the BAC at the time of measurement, and the corresponding interval on the BAC curve (rising limb, peak, or declining limb), and (iv) the potential risk factors under investigation. Overall, the specificity gained with these changes will be crucial for convergence and integration of future research. Second, while evidence for a low level of response to alcohol's more sedative and sluggish effects to relate to future alcohol disorders are without question, the scope of this research would be enhanced by inclusion of reliable and valid measures of the rewarding and positive-like alcohol effects during early to peak BAC (Martin et al., 1993). Finally, at the same time, research examining persons who may be at risk for future alcohol dependence by virtue of drinking phenotype will remain limited without better translational models to address whether the heightened positive and reduced sedative effects are inherent or whether they develop over repeated exposures (i.e., sensitization, tolerance). Therefore, as mentioned earlier, it will be crucial to bring together human and animal research to address such issues, expand measurement of hedonic and rewarding alcohol effects in the animal paradigm, and incorporate the expansion and availability of increasingly sophisticated technologies and prospective designs to expand the focus in this area.

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