## COMMENTARY

# The Answer You Get Depends on the Question You Ask

Marc A. Schuckit

The article by King *et al.* (1) has many strengths and raises issues relevant to substance use disorders and psychiatry overall. The goal was to identify characteristics that contributed to future alcohol problems and heavy episodic drinking (i.e., binges) in 104 heavier drinking subjects aged 21 to 40 (mean age 25). Predictors of these outcomes included feelings of sedation, stimulation, and liking and wanting more alcohol after drinking and at a breath alcohol level (BrAC) of ~80 mg/dL. Relationships between predictors and outcomes were analyzed using 1) general estimating equations with all 104 subjects, asking if each baseline characteristic predicted adverse outcomes; 2) trajectory groups (e.g., the 10 subjects with the most severe outcome who carried the greatest weight in this step); and 3) exploratory cluster analyses to identify subgroups of relationships between predictors and outcomes. Analyses were well done, follow-up rates were excellent, and the authors concluded that in this population alcohol stimulation and reward sensitivity best predicted alcohol problems and heavy episodic drinking.

The process of framing questions, selecting study populations, choosing analytic strategies, and interpreting results includes common challenges when evaluating predictors (and possibly causes) for substance-related and psychiatric outcomes. Most symptoms and disorders in our fields are complex genetically influenced conditions where multiple sets of genes contribute to intermediate characteristics that increase or decrease the risk for the syndrome of interest (e.g., anxiety, depression, or substance use and related problems) (2). There is no perfect way to execute this type of research, and in light of the complexities, no single study can evaluate all components of a broad question.

To place the article under discussion into perspective, it is important to remember that multiple intermediate characteristics impact on heavier drinking and alcohol problems at different stages of a person's life (2,3). An individual's response to alcohol is only one of several complex factors that contribute to the likelihood of drinking more or less per occasion and to the risks for alcohol problems. There are also multiple types of alcohol responses, including a low level of response (LR) likely to be seen at all aspects of the BrAC curve, the stimulating effects of this drug, and heart rate responses to an alcohol challenge, as discussed in our recent letter to the editor (4). The study of any risk factor for adverse alcohol outcomes requires evaluations as early in the drinking career as possible and before an alcohol use disorder (AUD) and associated physiologic and attitudinal changes have developed in the context of heavy drinking. For example, the impact of a low LR to alcohol has been evaluated in drinkers as young as age 12 using a retrospective questionnaire regarding the drinks required for effects and at age 18 for challenges with nonbeverage alcohol (5), after obtaining the same type of informed consent as would be needed for a cocaine challenge or a liver biopsy.

Our own work asks a different question than was posed by King *et al.* (1). We have focused on the issue relevant to clinicians and prevention researchers regarding who among a broad range of nonalcohol-dependent young drinkers are more and less likely to drink heavily in the future. Youth is important here because the onset of alcohol dependence is usually around age 23 to 25 years, and by age 30, >80% of the risk for AUDs has passed. Recognizing the complexity of risk factors and the imperfections in any single type of measure, our alcohol challenges have included electroencephalogram, hormone, motor performance, and functional magnetic resonance imaging measures as markers of a low LR [e.g., (2,4,6)]. To evaluate genetic contributors to LR and identify environmental mediators of its effects in large samples, for our 30-year follow-up of >1500 subjects from 450 families and in >1900 subjects followed from age 12 to 18 in the United Kingdom, we also developed a self-administered questionnaire regarding the number of drinks required for a range of effects [e.g., (7)]. The identification of environmental partial mediators of the impact of the low LR on future drinking led to a prevention trial evaluating whether teaching 18-year-old drinkers about the risks associated with the low LR can help modify their drinking (8).

The article by King *et al.* (1) is consistent with additional studies in demonstrating that some people may have a heightened stimulating response to alcohol that is also associated with future heavy drinking (9). Enhanced positive sensations at rising BrAC levels and less negative sensations at falling levels has been called a differentiator model of the risk for heavy drinking (9,10). When our work with LR began in the 1970s, our subjective measure of response included several items that incorporate some stimulant-like feelings (e.g., feeling high, drunk, effects of alcohol) at 15 minutes, 30 minutes, and ~ every half hour over 3 hours in our typical alcohol challenge paradigm. However, the same subjects who reported a low response to sedative-like effects (e.g., feeling sleepy, dizzy, clumsy) reported low LRs for the more general high, drunk, and drug effect items at eight rising, peak, and falling time points. In fact, these more generic intoxication feelings, rather than the sedative-like effects, most closely reflected the risk for future heavy drinking. If we had observed the same stimulant responses noted by King *et al.* (1), these scores would have been included in our evaluations of genetic and environmental mediators and in our trajectory analyses. However, no one can adequately evaluate everything and when our prospective work began in 1978, we did not include the more sensitive stimulating measures used by King *et al.* (1). Their work demonstrates that there is likely to be a subset of drinkers with exaggerated stimulatory responses to alcohol that contribute to their continued heavy drinking.

This brings me back to the question of what exactly the King *et al.* (1) article found and how it might be interpreted. Perhaps the most salient issue is that the question I have been asking

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addresses the predictors of future heavy drinking and alcohol problems in a broad range of nonalcoholic drinkers as young as age 12. However, reflecting the authors' emphasis on a different question, their study evaluated the role of alcohol-related sedating, stimulating, wanting more, and liking in individuals after excluding 86 subjects with the lightest drinking and the potentially highest LR to alcohol. Similar restrictions were apparently not made for the range of stimulating, liking, or wanting effects, making it difficult to compare the performance of those predictors with the restricted range of the low LR regarding sedation. Despite these restrictions, it is worth noting that the *p* values associated with low sedating effects performed well compared with the stimulating effects in the generalized estimating equations analysis where all 104 subjects were included. Consistent with the issue that the answer you get depends on the question you ask and how you evaluate it, in the trajectory and exploratory cluster analyses, much of the weight was carried by the small subgroup of the 10 relatively heavy drinking subjects with the most consistently high problematic drinking during follow-up. A more robust evaluation of the relative impact of the self-reports of the sedating and stimulating effects of alcohol might be seen if the full range of the low LR was allowed to operate in these analyses by adding the 86 subjects with the light drinking and high sedation responses to the analyses, as those individuals represented almost half of the original participants. I am also a bit concerned that some of the subjects may have underreported their alcohol problems and actually met criteria for alcohol dependence at baseline, as participants reported up to 40 drinks per week (the latter would be ~7 drinks per day; double that if they consumed alcohol on only half of the days as indicated in this sample). The inclusion of drinkers with such high intake and prior potentially rewarding experiences with heavy drinking may have enhanced their responses to liking alcohol and wanting more, especially if some met criteria for an AUD at baseline. Finally, the absence of differences for sedation or stimulation on the rising and falling limbs of the BrAC curves may not support the differentiator model as defined in some other articles (9,10).

In closing, this is a fine and well-executed study with an impressive follow-up rate. The data add important information to the literature demonstrating that an enhanced stimulatory effect of alcohol is likely to be associated with a continuation of relatively heavy drinking and associated problems among more heavy drinkers who do not have a high sedation response. I look forward to larger studies with longer follow-ups of a broader range of drinkers that may serve as the basis for searching for additional genetic and environmental influences that contribute to the AUD risk. It is likely that an enhanced stimulation effect of alcohol may join studies of the importance of the genetically influenced characteristics of alcohol metabolism, several major psychiatric conditions, externalizing characteristics, and the low level of response to alcohol as risk factors for future heavy drinking (1).

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