Mechanisms of topiramate effects: refining medications development for alcoholism

The current issue of *Addiction Biology* includes two manuscripts examining the mechanisms of topiramate (TOP) effects on alcohol use. The study by Kranzler *et al.* (2014) describes analyses of nighttime drinking behavior among treatment-seeking patients during a 12-week randomized and controlled trial of topiramate (200 mg/day) for alcohol dependence. Following up on previous work from his group, Kranzler demonstrated that a genetic polymorphism (rs2832407) in the gene encoding the GluK1 kainate subunit (*GRIK1*) moderates response to topiramate such that C-allele homozygotes show lower levels of nighttime drinking across the 12-week trial. Interestingly, this study found that the pharmacogenetic effect (TOP × *GRIK1* SNP) on nighttime drinking was accounted for by mean ratings of self-efficacy. The study by Miranda *et al.* (2014), in turn, focuses on non-treatment-seeking heavy drinkers assessed in the laboratory and in the natural environment using ecological momentary assessment (EMA) during a 5-week trial of topiramate (200 mg/day). While probing for medication effects on subjective responses to alcohol and alcohol craving, both in the laboratory and in the natural environment, an interesting pattern of results emerged. Topiramate was found to attenuate alcohol craving during a drinking episode, which, in turn, accounted for medication effects on alcohol use during the trial.

These studies share a common focus on understanding the mechanisms by which topiramate may be an effective medication for alcoholism with the overarching goal of informing the use of topiramate through a personalized medicine approach. These two studies are methodologically sophisticated as they employ a host of techniques to assess both mechanisms and drinking behavior in a valid and reliable fashion, while also capturing the complex nature of these constructs. Kranzler and colleagues use interactive voice response (IVR) technology to obtain daily diary data in the context of a clinical trial, whereas Miranda and colleagues combine EMA assessments with human laboratory paradigms such as cue-exposure and alcohol challenge. One of the most notable strengths of both studies is their ability to test mechanisms in relation to carefully ascertained alcohol use over the course of each trial. As noted by Miranda and discussed in detail elsewhere (Ray, Hutchison & Tartter 2010), the association between a particular mechanism and alcohol use is often implied in human laboratory studies when in fact it should be explicitly examined. These two studies do a commendable job of

capturing the dynamic nature of constructs such as craving and self-efficacy, while interrogating the association between these putative mechanisms of action and alcohol use. Using mediational models, Kranzler *et al.* and Miranda *et al.* take this line of inquiry one step further by testing whether medication effects (TOP versus Placebo) on drinking outcomes are in fact explained, or mediated, by self-efficacy and alcohol craving, respectively. The level of methodological rigor in these studies sets the standard for future studies of mechanisms of action of pharmacotherapies for alcoholism.

In addition to learning from what these studies have in common, considering their differences may be equally important. To that end, the most notable distinction between these studies is that while Kranzler *et al.* enrolled treatment-seeking alcohol-dependent individuals, Miranda *et al.* recruited non-treatment-seeking heavy drinkers, most of whom were not alcohol-dependent. Let us consider the issues of treatment-seeking status and alcohol use trajectory in studies of pharmacotherapy for alcoholism. Treatment-seeking is a key construct in that when individuals enroll in a treatment study, it is presumed that their primary motivation is to reduce their drinking or to abstain from alcohol. Conversely, non-treatment seekers are drawn to participate for monetary reinforcement. The smoking cessation literature has recognized that treatment-seeking status affects responses to pharmacotherapy in the clinic and in experimental laboratory paradigms alike (Perkins, Stitzer & Lerman 2006). For example, an early meta-analysis of nicotine replacement trials found that efficacy was greater among individuals who self-referred to a trial than those who were invited from hospital clinics (Tang, Law & Wald 1994). In medications development for alcoholism, less is known about the impact of treatment-seeking status, and clearly, some outcomes may be more vulnerable to the effects of treatment-seeking status than others. Further, within treatment seekers, there is also variability in treatment goals, which, in turn, predicts clinical outcome (Bujarski *et al.* 2012). The key point being that treatment-seeking status and, more broadly, motivation to change alcohol use represent a continuous, and rather volatile, construct requiring closer consideration in medications development for alcoholism.

Next, let us examine the distinction between heavy drinkers and alcohol-dependent samples. The degree to which these samples can inform one another is poorly understood. Recently, it has been argued that even within

samples expressing an alcohol use disorder, there are distinct risk profiles that may be amenable to different pharmacological interventions (Heilig *et al.* 2010). Heavy drinkers without an alcohol use disorder may be most similar to individuals in early stages of alcoholism, although they appear to be distinct in key constructs including their subjective response to alcohol in the laboratory (Bujarski & Ray 2014). Studies enrolling individuals across a wide range of alcohol exposure may be necessary to fully describe alcohol phenotypes expressed over the course of one's drinking history. Nonetheless, in the interest of science that can more rapidly translate into more effective treatments, clinical cut-offs should be carefully considered. The non-treatment-seeking heavy drinkers enrolled in the trial by Miranda *et al.* clearly displayed variation in alcohol craving, which allowed for meaningful medication effects to be detected, although less so with regard to alcohol cue-reactivity. And while the goal is not to fully integrate the findings by both studies, considering their similarities and differences represents a useful exercise as we seek to synthesize the literature on topiramate, a medication with promising efficacy data yet poor utilization.

Lastly, an approach toward systematically examining mechanisms of medication effects would be advanced by an understanding of how these mechanistic variables relate to one another. For instance, would it be fair to say that alcohol craving is more proximal to alcohol use than subjective response to alcohol in the laboratory? That is a plausible hypothesis requiring further testing. Likewise, what would be the expected relationship between alcohol craving and self-efficacy? As aptly noted by Kranzler *et al.*, self-efficacy has some conceptual overlap with intention which health behavior theories typically place as the most proximal determinant of actual behavior. It is plausible that self-efficacy represents a meta-construct that can synthesize one's perception of his/her capacity to reach a drinking goal based on a host of subjective experiences (e.g. protracted withdrawal, urge to drink, affective state). Ultimately, a more complete theoretical model for how these mechanisms function as determinants of drinking and, in turn, how medications affect these mechanisms is needed. As indicated by both Kranzler *et al.* and Miranda *et al.*, the overarching goal of these efforts is to optimize, and even personalize, the treatment of alcoholism. Considering the dynamic nature of these mechanisms, captured using state-of-the-art methods in these two trials, within the context of progressive nature of alcohol dependence (i.e. from heavy drinking to late stage dependence) offers unique opportunities to determine which patients are better candidates for which pharmacotherapies. The two studies on the mechanisms of action of topiramate published in this issue of *Addiction Biology* set the stage for sophisticated trials combining biological, behavioral and clinical science in the interest of treatment development for alcoholism.

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