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Treatment for Alcohol Use Disorder: Progress in Predicting Treatment Outcome and Validating Non-Abstinent Endpoints

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An emerging framework for multimodal assessment of addictions (Kwako et al., 2016), and expanded definitions of acceptable endpoints for alcohol treatment trials (Food and Drug Administration, 2006) are informing efforts toward personalized treatment of alcohol use disorder (AUD). A critical issue in determining for whom an intervention will work lies in the definition of clinical trial endpoints. The six articles in this virtual issue of *Alcoholism: Clinical and Experimental Research* illustrate recent progress in identifying predictors of alcohol treatment outcome, and pioneering work on the stability and validity of promising non-abstinent (e.g., low-risk drinking) clinical trial endpoints. As a set, the articles highlight how definitions of AUD treatment outcomes or trial end-points can influence the identification of predictors of clinical course.

The first three articles in this virtual issue examine predictors of AUD treatment outcome that range from a novel neurocognitive indicator of social cognition (i.e., facial emotion recognition) (Rupp et al., 2017) to alcohol subtyping schemes that can be readily assessed in a clinical setting (Weinland et al., 2017) and neuroimaging measures of brain macrostructure (Durazzo and Meyerhoff, 2017). Importantly, the predictors of treatment outcome covered by the articles in this virtual issue represent multiple levels of analysis, from brain structure to behavior, and multiple domains of functioning (e.g., social cognition, executive functioning, affect regulation), as proposed in the Alcohol Addiction Research Domain Criteria (AARDoC) (Litten et al., 2015). Given the range of possible predictors of outcome, determining the most parsimonious set of measures, and the added value of more expensive and burdensome measures (e.g., neuroimaging) relative to self-report for predicting a specific outcome, is a high priority in improving clinical assessment.

The other three articles examine definitions of treatment outcome. Although addictions treatment has traditionally focused on a goal of abstinence, the US Food and Drug Administration (FDA), in a landmark shift, expanded acceptable alcohol clinical trial endpoints to include non-abstinent outcomes based on evidence of clinical benefit, defined

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as how an individual “feels and functions” (Food and Drug Administration, 2006, 2015). In addition to abstinence, the FDA currently accepts no heavy drinking days (i.e., no days on which women consume >3 drinks and men consume >4 drinks) as an alternative clinical trial endpoint (Food and Drug Administration, 2015). However, gaps remain regarding the clinical validity of no heavy drinking days as a clinical trial endpoint, as well as other endpoints. In this regard, two articles in this virtual issue used COMBINE study data (Anton et al., 2006), first, to examine the temporal stability of the no heavy drinking endpoint (Witkiewitz, Wilson, et al., 2017), and second, to determine the clinical validity of decreases in the World Health Organization (WHO) drinking risk categories as a type of non-abstinent clinical trial endpoint (Witkiewitz, Hallgren, et al., 2017). Importantly, analyses of change in WHO drinking risk categories could provide further support for non-abstinent endpoints, as well as the potential utility of a harm reduction approach for some individuals. The final article provides a rare look at the long-term predictive validity of adults with AUD who were classified as low-risk, abstinent, and heavy drinking using data collected over a 9-year follow-up period (Kline-Simon et al., 2017).

Predictors of treatment outcome

Reliable predictors of AUD treatment outcome can not only help to identify for whom an intervention may be most effective, but can aid in the early detection of potential non-responders, so that alternative interventions can be offered to meet specific needs. The inability to recognize emotions in others has been associated with interpersonal problems and poorer alcohol treatment outcomes in cross-sectional research (Kornreich et al., 2016). In one of the first studies to prospectively investigate neurocognitive social abilities as predictors of alcohol treatment outcome, Rupp and colleagues (2017) compared patients with AUD who completed inpatient treatment without relapsing (n=45; completers) with patients who relapsed during treatment or dropped out of treatment (n=11; non-completers). Compared with treatment completers, non-completers showed poorer facial emotion recognition at treatment onset, particularly with respect to disgust, anger, and neutral emotion faces. In their predominantly male sample, the two groups did not differ on characteristics that could explain the group difference on emotion recognition ability, including psychiatric comorbidity, medication use, alcohol-related characteristics, and general cognitive measures. These findings suggest the potential for objective assessment of facial emotion recognition to identify patients at risk for worse treatment outcomes.

In a different approach to predicting AUD treatment outcome, Weinland and colleagues (2017) used alcohol subtyping schemes, rather than focusing on one domain of functioning, to identify a cluster of features that predict outcome. Prior work using Cloninger type 1/2 characteristics (Irwin et al., 1990) and the Lesch typology (Lesch et al., 1990) to predict treatment outcome found that patients classified as Cloninger type 2 (early onset of heavy drinking, more severe alcohol dependence than type 1) and Lesch type 4 (perinatal damage, severe cerebral disease) had lower rates of abstinence over 3-month follow-up than patients classified as Lesch type 2 (drinking to reduce anxiety) (Pombo et al., 2015). Weinland and colleagues (2017) extended this work over a longer follow-up period, and found that patients with >1 hospital readmission had higher Cloninger type 2 scores than non-readmitted patients, an association that was stronger in females. Regarding the Lesch subtypes, patients

classified as type 2 (drinking to reduce anxiety) had lower risk for readmission, fewer readmissions, and more days to first readmission than patients classified as the other Lesch subtypes, consistent with prior work (Kiefer et al., 2005; Pombo et al., 2015). These results suggest that Cloninger type 2 scores and Lesch subtypes show some promise in identifying patients, particularly females, at risk for hospital readmission after detoxification.

Moving from the behavioral level of analysis to the level of brain and neuroimaging measures, brain macrostructural features have also been found to predict AUD treatment outcome. For example, at treatment entry, individuals who relapse, compared to those who abstain for at least 3 months, have thinner cortices, and smaller surface areas and volumes mainly in anterior frontal brain regions, such as the anterior cingulate cortex (Rando et al., 2011) and dorsolateral prefrontal cortex (Durazzo et al., 2011; Rando et al., 2011; Seo and Sinha, 2015). In this issue, Durazzo and Meyerhoff (2017) reported outcomes for a sample of 129 mostly male veterans in outpatient AUD treatment, most (75%) of whom resumed drinking within 6 months after treatment. Over 18-month follow-up, 82 relapsed (returned to any alcohol use) and 47 abstained; smokers and those with a medical condition relapsed earlier. Smaller volumes of the right caudal ACC, right rostral ACC, and lower total right frontal gray matter volume, predicted relapse over follow-up, over and above mood disorder (particularly major depression), and lower education (<15 years). Thus, decreased macrostructural integrity, specifically smaller volumes of the right rostral and caudal ACC and total right frontal gray matter at treatment entry, in addition to psychiatric and demographic characteristics, could serve as markers of relapse risk.

Interestingly, when considered together, the Rupp et al. (2017) and Durazzo and Meyerhoff (2017) studies suggest some intriguing possible links between social cognition deficits and prefrontal dysfunction in AUD that have been discussed elsewhere in the literature (Alba-Ferrara et al., 2016; Uekermann and Daum, 2008; Wilcox et al., 2016). For example, a prospective study of emotion recognition and AUD treatment outcome found that greater rostral ACC activation in response to aversive face processing was associated with better treatment outcome (Charlet et al., 2014). Although Durazzo and Meyerhoff (2017) focused on brain structure, identifying smaller volumes of the right rostral and caudal ACC as predictors of relapse, and did not examine regional activation, convergence on this brain-behavior link in relation to treatment outcome could inform the development of novel neuroscience-informed social cognitive interventions for AUD. Future studies are indicated that explore these potential links between deficits in social cognition and AUD.

Other important emerging predictors of treatment outcome that are being investigated include, for example, neuroimaging-based markers, and genetics and pharmacogenetics. There is growing interest in using functional neuroimaging paradigms such as cue-elicited brain activation (Lukas et al., 2013; Schacht et al., 2013; Wilcox et al., 2013) and response inhibition (Zilverstand et al., 2018) to identify predictors of treatment response (see (Courtney, 2016) for a review; (Chung et al., 2017) for a special issue). Although neuroimaging data currently cannot be used to predict individual outcomes, a computational approach (e.g., Bayesian model selection, generative embedding) has been proposed to have utility for single-subject prediction of clinical outcomes (e.g., (Stephan et al., 2017)). As another important predictor of treatment outcome, genetic risk for AUD has been extended

to research on pharmacogenetics (Cservenka et al., 2017; Jones et al., 2015), which has shown promise for medications such as Naltrexone in interaction with *OPRM1* genotype in treating AUD (Anton et al., 2008) and smoking (Schacht et al., 2017). Neuroimaging and pharmacogenetic methods also have been combined to gain insight into neurobiological mechanisms by which medications reduce heavy drinking (e.g., (Weerts et al., 2013) see (Falcone et al., 2013) for a review). A further consideration is that dual diagnosis patients (e.g., co-occurring depression, PTSD, ADHD), a subgroup at high risk for relapse (Bradizza et al., 2006), warrant consideration because emerging research suggests that these patients might have differential response to certain types of treatment, particularly pharmacological interventions (e.g., (Arias et al., 2014)).

Some caveats need to be considered when interpreting results of research on predictors of AUD treatment outcome. Specifically, the high proportion of male patients in treatment-seeking samples limits generalizability of results to females. Sample sizes can be relatively small, such that comparisons between those who abstain versus relapse may have limited statistical power. Finally, comparisons across studies can be challenging due to differences in the outcome predicted (e.g., any alcohol use, treatment dropout) and the length of follow-up.

Stability and validity of abstinent, low-risk drinking, and heavy drinking outcomes

Because one heavy drinking day could represent an isolated event, rather than a relapse (i.e., a return to a regular pattern of heavy drinking) (Witkiewitz and Marlatt, 2007), the stability or persistence of heavy drinking needs to be considered when using this as a marker of treatment response. Witkiewitz, Wilson, and colleagues (2017) used COMBINE study data (n=1,383) (Anton et al., 2006) to model transitions into and out of any heavy drinking (i.e., ≥4/5 standard drinks in a day for women/men) and no heavy drinking (low-risk drinking or abstinence) across three time frames: during treatment (months 1–4), the transition out of treatment (months 4–7), and up to 12 months post-treatment (months 13–16). Patients who showed stability in no heavy drinking days during the first 3 months of treatment had a lower probability of shifting to a heavy drinking outcome later, suggesting that after an initial 3-month period, no heavy drinking days could be a primary outcome. The probability of transitions occurring across consecutive months decreased by almost half, from 16.3% in months 4–5 to 9.4% in months 15–16. Among those classified as heavy drinking (i.e., a “non-responder”), there was heterogeneity in post-treatment patterns of alcohol use, with the vast majority of individuals achieving clinically meaningful reductions in heavy drinking from baseline levels. Importantly, although classified as a “non-responder” based on any heavy drinking, most showed reductions in heavy drinking from baseline levels that support harm reduction as an alternative outcome to abstinence.

In the second set of COMBINE study analyses, Witkiewitz, Hallgren and colleagues (2017) examined the clinical validity of reductions in the WHO drinking risk levels (very high risk, high risk, moderate risk, and low risk) as clinical outcomes in relation to meaningful decreases in negative alcohol-related consequences and mental health symptoms during

treatment and at one year follow-up in patients with AUD. Results showed that a 1-shift reduction in WHO risk drinking levels from baseline to end of treatment was associated with significantly fewer alcohol-related consequences and better mental health, and that these improvements remained up to 1 year following treatment. Further, greater reductions in WHO risk levels predicted greater improvements in functioning. These results also support the validity of a harm reduction alternative to abstinence as a possible endpoint in alcohol clinical trials.

To better understand long-term treatment outcomes, Kline-Simon and colleagues (2017) classified adults in day treatment for AUD six months after intake (n=1061) as abstinent, low-risk (i.e., non-abstinent, no days when ≥5 drinks consumed), or heavy drinking (i.e., >1 day when ≥5 drinks consumed). Over 9-year follow-up, abstainers and low-risk drinkers reported better drinking outcomes than heavy drinkers, and abstainers had better drinking outcomes than low-risk drinkers. Of note, low-risk drinkers, compared to abstinent or heavy drinkers, were more likely to be female; and heavy drinkers were more likely to be younger. In terms of psychiatric outcomes, abstainers and low-risk drinkers fared better than heavy drinkers. For family/social outcomes, abstainers had better outcomes than heavy drinkers. Abstainers and low-risk drinkers did not demonstrate reliable differences across the psychosocial outcomes examined. Medical outcomes did not differ across the three groups at 9-year follow-up. Results suggest that low-risk drinking, in addition to a goal of abstinence, may show benefit across a range of psychosocial and psychiatric outcomes over an extended follow-up period for some individuals in treatment for an AUD.

Recent findings regarding the stability of low-risk drinking during and following treatment (Witkiewitz, Wilson, et al., 2017), and relatively favorable outcomes of low-risk (versus heavy) drinking through longer-term follow-up (Kline-Simon et al., 2017), provide further support for the usefulness of a non-abstinent, harm reduction-based outcome (e.g., low-risk drinking) for some individuals. Abstinence represents a strict standard for clinical benefit, which can be challenging to sustain for a lifetime and may not be a patient's desired outcome. As the articles in this virtual issue demonstrate, many individuals can reduce and maintain reductions in alcohol use. For some individuals, reduced drinking could serve as an intermediate step to abstinence (Gastfriend et al., 2007). Non-abstinent drinking goals, such as low-risk drinking, could engage more individuals in treatment, and expand the settings in which alcohol treatment is offered (e.g., primary care) (Rehm et al., 2016). An important limitation of the studies in this virtual issue is that abstinence, rather than a reduction in drinking, was generally the intended treatment outcome. Critical questions for future research are who would benefit from a goal of abstinence compared with other outcomes, such as low-risk drinking, and how these low-risk drinking outcomes operate in the context of treatment designed to promote low-risk drinking.

To date, alcohol clinical trials have focused on the endpoints of abstinence, low-risk drinking, the absence of heavy drinking days, and percent heavy drinking days. A reduction in WHO drinking risk levels provides a novel, alternative non-abstinent endpoint that has shown clinical validity in an alcohol treatment (Witkiewitz, Hallgren, et al., 2017) and a general population sample (Hasin et al., 2017). As another possible non-abstinent endpoint, DSM-5 AUD total criteria count and severity category (i.e., mild, moderate, severe) showed

potential as alcohol treatment outcome indicators in a randomized clinical trial, such that higher total criteria count and severity category were associated with less abstinence, more heavy drinking, and more negative consequences over 6-month follow-up (Kiluk et al., 2018). A caveat of using a continuous measure like total criteria count or percent heavy drinking days as an outcome indicator is that the number of individuals who respond to treatment cannot be conveyed as easily relative to a categorical measure (relapse: yes/no) of treatment response.

There is a continuing need to validate other reduction-based indicators in terms of reliability, validity, and clinical benefit in relation to a range of relevant measures of meaningful improvement in functioning (e.g., physical health, social functioning). A new national, cross-sectional study examined associations between recovery (i.e., the first 5 and 40 years since resolving an alcohol or drug problem) and measures of well-being (e.g., self-esteem, happiness) (Kelly et al., 2018). Over the first 5 years, initial drops in self-esteem and happiness, were followed by increases, whereas over 40 years, there were initially steep increases in well-being in the first six years, followed by shallower increases in well-being (Kelly et al., 2018). The changes in measures of well-being over shorter and longer-term recovery emphasize the importance of monitoring non-abstinence indicators of well-being, and effectively managing challenges during early recovery (Kelly et al., 2018). Notably, meaningful reductions in alcohol consumption could occur in the absence of improvement on indicators such as medical outcomes (Palpacuer et al., 2015), as found in the Kline-Simon et al. study (2017) in this issue. Thus, indicators of clinical benefit need to be sensitive to detecting relevant improvement during the study time frame. The most appropriate indicator of benefit also depends on the specific level of analysis (e.g., brain to behavior) and particular domain of functioning (e.g., executive functioning) that is of interest, and how the intervention is hypothesized to produce benefit (Stockings and Farrell, 2017).

Another key issue involves shifting to the study of “change points” in clinical course, rather than focusing on a single endpoint or outcome (i.e., lapse or relapse). Recovery reflects a process of change, and clinical trials capture a limited slice of that process. Notably, the three studies on predictors of treatment outcome in this virtual issue differed in the outcomes examined: treatment dropout or relapse during treatment (Rupp et al., 2017), treatment readmission (Weinland et al., 2017), and return to any alcohol use over follow-up (Durazzo and Meyerhoff, 2017). Further, research shows that predictors differ for specific change processes. For example, variables that predicted post-treatment drinking status (e.g., mood disorder) differed from variables that predicted time to first alcohol use (Durazzo and Meyerhoff, 2017). The articles in this issue examining non-abstinent (e.g., low-risk drinking) endpoints pave the way for research on predictors of treatment outcome, like clinical trials, to include analyses of non-abstinent outcomes, such as reductions in WHO drinking risk levels (Witkiewitz, Hallgren, et al., 2017), in addition to abstinence-based outcomes (e.g., time to first drink, any alcohol use).

The way in which outcomes or endpoints are defined can have important implications for identifying predictors of clinical course. Outcomes vary not only in terms of what is assessed (e.g., drinking risk level, quality of life), but in parameters such as the threshold

used to define the outcome (e.g., continuous versus dichotomous) and minimum time frame considered (e.g., time required to show stability of a given behavioral pattern). In addition, decisions need to be made regarding how to handle missing data, for example, continuous versus categorical variables when key defining data (e.g., alcohol use) are missing secondary to dropout or other reasons. Decisions regarding the definition of the endpoint can affect the strength of the association between the variables, and thus, the ability to identify predictors of treatment outcome.

Future research will benefit from new tools, such as smartphones (e.g., apps to deliver surveys), wearable technology (e.g., activity trackers), and biosensors (e.g., transdermal alcohol sensors) that can provide closer to real-time monitoring across many of the AARDoC domains at the behavioral level. These new tools promise to fill in gaps in our understanding of the dynamic interplay of personal and contextual factors that enhance or erode self-efficacy to achieve and maintain drinking reduction goals (Bae et al., 2018; Carreiro et al., 2018; Tomko and McClure, 2018). Further, the use of alcohol biomarkers (e.g., serum carbohydrate-deficient transferrin, whole blood phosphatidylenthanol, urine ethyl glucuronide) will enhance the validity of self-reported drinking data, help to identify individuals who may be in need of alcohol treatment, and allow clinicians and researchers to better monitor patient progress during treatment (Helander et al., 2012; Litten et al., 2010; Piano et al., 2017). Finally, new data analytic techniques (e.g., machine learning; (Acion et al., 2017)) show promise for improving our ability to predict AUD treatment success, especially in analyses of multi-domain (e.g., genes, brain, behavior) and potentially intensive longitudinal streams of data.

The articles in this virtual issue show that while progress has been made in identifying predictors of treatment outcome, the practical clinical utility of the predictors is limited by their accuracy, expense, and burden when implemented in the treatment setting (Weinland et al., 2017). In this regard, there is still much to be done, for example, in testing and refining the multimodal Addictions Neuroclinical Assessment framework that is proposed for use in personalized interventions (Kwako et al., 2016). Importantly, refining clinical assessment could lead to novel therapies that target specific mechanisms (e.g., facial emotion recognition) and individual needs. In terms of clinical course, a consensus is developing regarding the need to standardize and validate non-abstinence (e.g., low-risk drinking, reduction in WHO risk drinking level) endpoints (Stockings and Farrell, 2017), which could reduce barriers to treatment for individuals who want to reduce their drinking, rather than completely abstain; and could facilitate comparison of alcohol clinical trials internationally. Predicting who would benefit from a goal of abstinence and who might be appropriate for a non-abstinent, low-risk drinking goal remains a priority for future research.

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