CRITICAL REVIEW

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Beyond mediators: A critical review and methodological path forward for studying mechanisms in alcohol use treatment research

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Abstract

Understanding how treatments for alcohol use disorder (AUD) facilitate behavior change has long been recognized as an important area of research for advancing clinical care. However, despite decades of research, the specific mechanisms of change for most AUD treatments remain largely unknown because most prior work in the field has focused only on statistical mediation. Statistical mediation is a necessary but not sufficient condition to establish evidence for a mechanism of change. Mediators are intermediate variables that account statistically for the relationship between independent and dependent variables, whereas mechanisms provide more detailed explanations of *how* an intervention leads to a desired outcome. Thus, mediators and mechanisms are not equivalent. To advance mechanisms of behavior change research, in this critical review we provide an overview of methodological shortfalls of existing AUD treatment mechanism research and introduce an etiologically informed precision medicine approach that facilitates the testing of mechanisms of behavior change rather than treatment mediators. We propose a framework for studying mechanisms in alcohol treatment research that promises to facilitate our understanding of behavior change and precision medicine (i.e., for whom a given mechanism of behavior change operates and under what conditions). The framework presented in this review has several overarching goals, one of which is to provide a methodological roadmap for testing AUD recovery mechanisms. We provide two examples of our framework, one pharmacological and one behavioral, to facilitate future efforts to implement this methodological approach to mechanism research. The framework proposed in this critical review facilitates the alignment of AUD treatment mechanism research with current theories of etiologic mechanisms, precision medicine efforts, and cross-disciplinary approaches to testing mechanisms. Although no framework can address all the challenges related to mechanisms research, our goal is to help facilitate a shift toward more rigorous and falsifiable behavior change research.

INTRODUCTION

Evidence-based alcohol use disorder (AUD) treatments include pharmacological and psychological interventions, such as naltrexone, acamprosate, cognitive behavioral therapy (CBT), family therapies, mindfulness-based treatments, and motivational interviewing/ enhancement therapy (Ray, Bujarski, et al., 2019). These treatments demonstrate comparable short-term efficacy (Boness et al., 2023; Tanner-Smith et al., 2016; Witkiewitz et al., 2019), and there is a need to better understand *how* a given treatment works and *what specific ingredients* make particular treatments effective for *whom* (Witkiewitz et al., 2022). Identifying the specific mechanisms by which AUD treatments yield beneficial effects has therefore become a major focus in addiction research. Referred to as "mechanisms of behavior change" (MOBC), these mechanisms span psychological, social, and neurophysiological processes (Nielsen et al., 2018).

Although often used synonymously, mechanisms and mediators are not equivalent. Mediators are intermediate variables that statistically account for the relationship between an independent and dependent variable, whereas mechanisms provide nuance on *how* an

intervention leads to a desired outcome. Criteria for establishing a mechanism are (1) strong associations, (2) specificity in the association between a behavior change ingredient and a mechanism and the associations between the mechanism and outcome(s) of interest (i.e., *a* and *b* paths, respectively, in Figures 1 and 2), (3) a gradient (i.e., dose response), (4) temporal relations (i.e., intervention affects the mechanism, which affects the outcomes), (5) consistency, or replication, of associations, (6) experimental designs, and (7) plausibility and coherence of the proposed mechanism (Hill, 1965; Kazdin & Nock, 2003). Prior reviews of studies examining why AUD interventions result in behavior change note that most studies examined mediators rather than mechanisms (Magill et al., 2020; Meisel et al., 2022).

Understanding MOBC can also guide the intervention dissemination by ensuring that the most effective components for a given person are delivered, thus efficiently maximizing treatment effects (Magill et al., 2023). This type of scaling may also reduce treatment costs and increase access (e.g., via shorter treatment durations; Schleider & Beidas, 2022). Understanding which treatment components are most effective is especially important given the large number of psychotherapies, many of which have common core
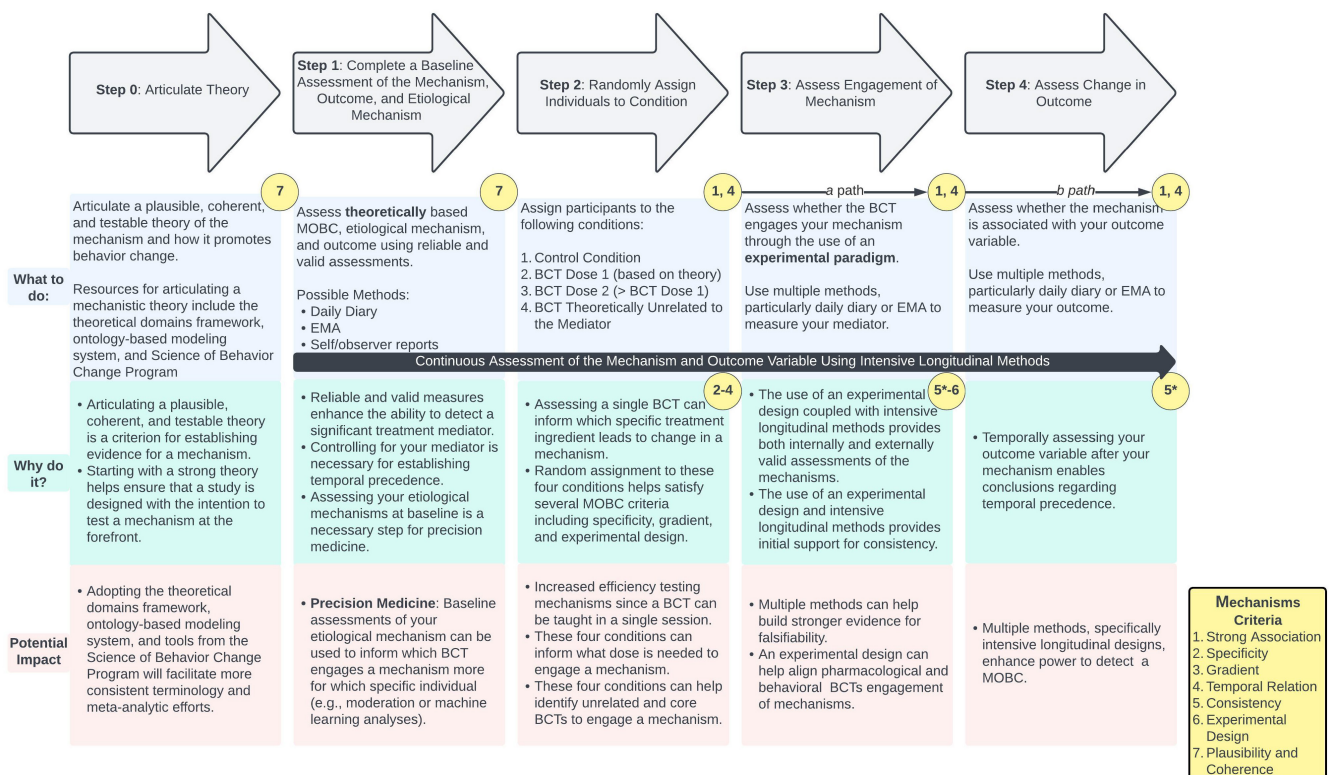
FIGURE 1 Methodological steps in an etiology-informed precision medicine approach to studying mechanisms in alcohol use treatment research. *No single study can satisfy the mechanism criteria of consistency. Replication across studies is needed to meet this criteria. However, replication across methods within a single study would provide initial support for consistency. BCT(s), behavior change technique(s); EMA, ecological momentary assessment; MOBC, mechanism of behavior change.

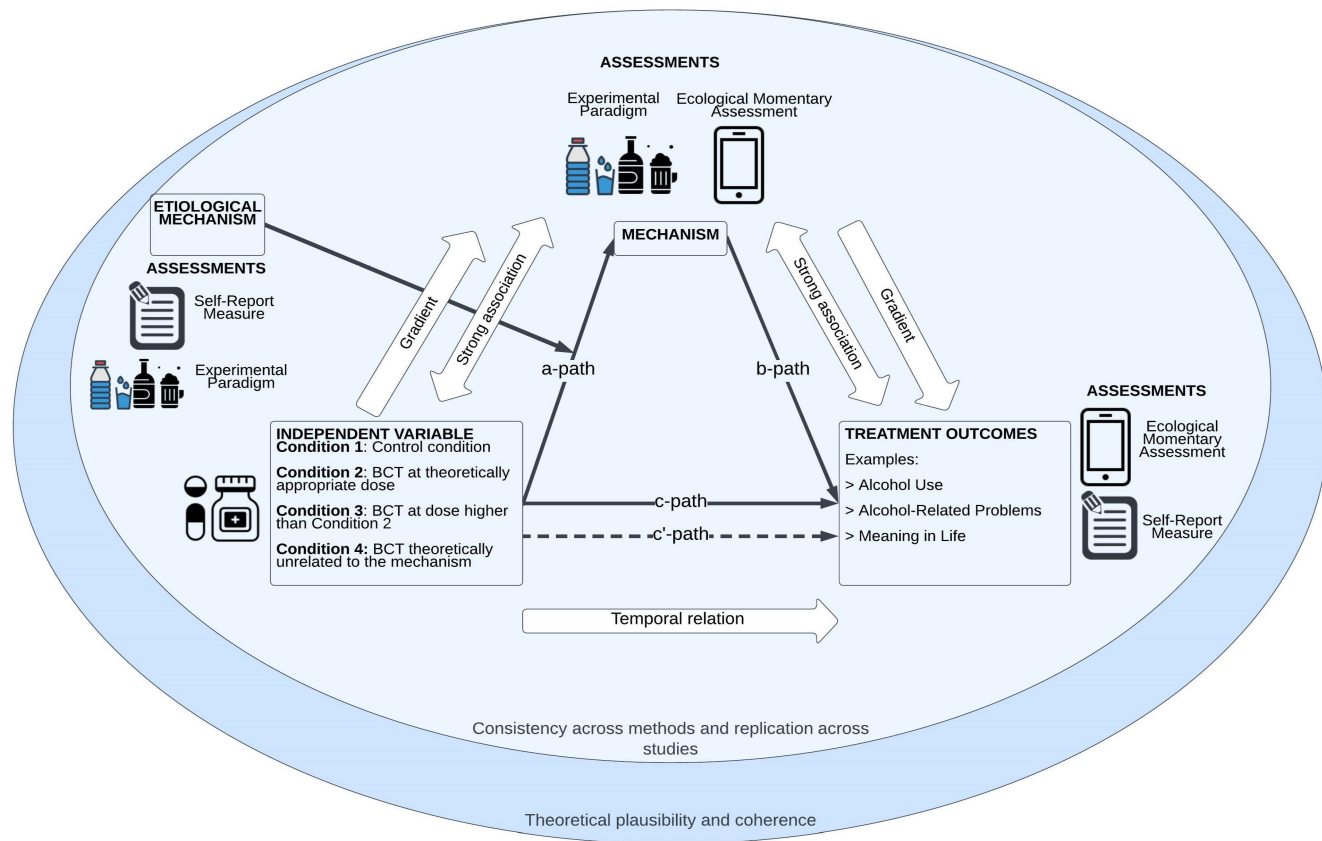**FIGURE 2** Conceptual figure of an etiologically informed precision medicine approach to studying mechanisms.

components (Hogue et al., 2017; Kazdin & Nock, 2003). Identifying these components can bring order and parsimony to existing treatments, which may guide other important efforts, such as therapist training and implementation (Hogue et al., 2017). Going further, understanding which treatment components are most effective *for whom* is likely even more beneficial for maximizing treatment effects (Boness & Witkiewitz, 2023). Yet, despite decades of research, the specific MOBC for most treatments remain largely unknown (Cuijpers et al., 2019; Magill et al., 2020; Meisel et al., 2022; Witkiewitz et al., 2022).

Current critical review

This critical review briefly details the major challenges to mechanism research in addiction science. Given other recent reviews (e.g., Meisel et al., 2022; Witkiewitz et al., 2022), we will not reiterate the evidence for and against specific mechanisms. Rather, to advance research on behavior change and identify viable next steps in elucidating how efficacious interventions yield beneficial effects, we offer an etiologically informed precision medicine approach to study behavior change in AUD treatment. We outline a methodological framework that facilitates testing MOBC, rather than solely testing treatment mediators, and advances our understanding of how and for whom a given mechanism of behavior change operates. In

addition, we offer examples testing MOBC in pharmacological and behavioral AUD treatments.

Identifying the processes that produce beneficial AUD treatment outcomes requires appropriate theory, measurement precision, sound research design and methodology, and robust statistical approaches. In the sections that follow, we critically review the literature that describes weaknesses in each of these areas and note how such weaknesses directly limit the impact of research on MOBC in AUD treatments (see Table 1). Although our focus is primarily on AUD, much of what we cover is relevant to addiction more broadly.

Theory

Comprehensive theory

Testing MOBC first requires a comprehensive and specific theory about the associations between the active treatment ingredient, specific mechanism of change, and a given outcome (see Figures 1 and 2 *a*- and *b*-paths). Such theories should be plausible and coherent, meaning they are reasonable given other existing theories and research (Hill, 1965; Kazdin & Nock, 2003), as well as testable (Longabaugh & Wirtz, 2001). A comprehensive theory of change also requires specificity about how a given mechanism operates as

TABLE 1 Criticisms of mechanism research and corresponding steps in the proposed framework.

Criticisms of mechanisms research	Citations from reviews, meta-analyses, and commentaries		Step in the proposed framework where addressed
Theory			
Comprehensive theory	• Black & Chung, 2014	• Nielson et al., 2018	Steps 0–4
	• Carroll & Kiluk, 2017	• Witkiewitz et al., 2022	
	• Magill et al., 2020		
	• Magill & Longabaugh, 2013		
Measurement & Assessment			
Reliable, valid, and temporally sequenced measurement	• Kelly et al., 2009	• Morgenstern & Longabaugh, 2000	Steps 1–4
	• Kelly, 2017	• Nielson et al., 2018	
	• Magill et al., 2015	• Black & Chung, 2014	
	• Meisel et al., 2022	• Reid & Carey, 2015	
Measuring etiological mechanisms	• Boness & Witkiewitz, 2023	• McCrady, 2017	Step 1
Research Design & Methodology			
Consideration of context for testing mechanisms	• Longabaugh et al., 2005	• Morgenstern & Longabaugh, 2000	Steps 1–4
	• Magill et al., 2020	• Nielson et al., 2018	
	• Magill & Longabaugh, 2013		
Need for greater specificity	• Longabaugh, 2007	• Meisel et al., 2022	Steps 1 and 2
	• Magill & Longabaugh, 2013	• Nielson et al., 2018	
Consideration of dose	• Kazdin, 2007	• Morgenstern & Longabaugh, 2000	Step 2
	• Magill & Longabaugh, 2013	• Reid & Carey, 2015	
Experimental designs	• Nielson et al., 2018	• Witkiewitz et al., 2022	Step 3
Statistical Methods			
Power	• Magill et al., 2020	• Morgenstern & Longabaugh, 2000	Steps 1–4
	• Meisel et al., 2022		
Outcome distributions	• Witkiewitz et al., 2015		Not addressed in the proposed framework[a]
Moving beyond simple mediation models	• Magill et al., 2015	• Reid & Carey, 2015	Not addressed in the proposed framework[a]
	• Morgenstern & Longabaugh, 2000	• Witkiewitz et al., 2022	
	• Meisel et al., 2022		

[a]Our proposed framework provides methodological, rather than statistical, recommendations for testing mechanisms. However, the design features of our methodological framework facilitate the use of advanced analytic methods for testing mechanisms (e.g., time-varying effect modeling and person-specific machine learning models).

part of a larger causal chain of sequenced and interacting processes, including contextual and temporal processes, to produce a certain treatment outcome among a given population (microprocesses or molar behavioral processes; Black & Chung, 2014; Witkiewitz et al., 2019). Without a comprehensive theory, it is difficult to characterize how and why behavior change occurs (Magill et al., 2020).

Two complementary starting points for behavior change-related theory selection and refinement are the Theoretical Domains Framework (see Cane et al., 2012; Michie et al., 2005) and the Ontology-Based Modeling System for behavior change theories (Hale et al., 2020; West et al., 2019). In brief, behavioral and implementation researchers developed the Theoretical

Domains Framework through a consensus-based process with the goal of integrating and synthesizing cross-disciplinary behavior change theories and improving the accessibility of this information. The framework integrates 128 theoretical constructs from 33 theoretical models of behavior change into 14 domains (e.g., emotion, motivation, and social processes) and can be used to identify influences on behavior and behavior change techniques (Atkins et al., 2017). Using the Theoretical Domains Framework, van Agteren et al. (2018) identified four domains (e.g., *knowledge* about smoking cessation, *skills* to reduce smoking, *beliefs in capabilities* to reduce smoking, and *behavioral regulation* to monitor their behaviors), which guided the evidence-based BCTs included in their smoking cessation mobile application. The Ontology-Based Modeling System, also developed through expert consensus, aims to standardize theoretical models of mechanistic behavior change processes (e.g., Theory of Planned Behavior) and integrate constructs across theoretical models by breaking them down into specific associations (e.g., "subjective norms positively influence intentions"). These associations are searchable at https://theory-database.appspot.com/. The Theoretical Domains Framework and Ontology-Based Modeling System reflect comprehensive approaches that could facilitate uniform mechanism terminology and theory testing across disciplines. We recommend that researchers use these systems, or their own extensions of these systems, to characterize a comprehensive theory for their target mechanisms.

Measurement of mechanisms

Reliable, valid, and temporally sequenced measurement

To effectively capture theoretical associations between specific treatment components and MOBC, it is critical that both the treatment component(s) and putative mechanism(s) are measurable (i.e., clearly operationalized) and quantified using reliable and valid instruments appropriate for the population and setting (Hallgren et al., 2018; Meisel et al., 2022). Otherwise, findings could be an artifact of measurement error (Morgenstern & Longabaugh, 2000).

Critically, the temporal sequence (i.e., timing) of measurement must be appropriate for capturing relevant treatment components (*a* and *b* path, Figure 2) and putative MOBC (Hallgren et al., 2018; Hopwood et al., 2021; Meisel et al., 2022). For example, causal inference requires a hypothesized mediator to temporally proceed the outcome (Kazdin, 2007). Reid and Carey (2015) reviewed 61 college student alcohol treatment trials and found only 36% assessed the mediator before the outcome. Theoretical models of the timing of relevant change processes in the mechanisms and outcomes should guide the measurement time frame of all constructs in a mechanistic process (Hopwood et al., 2021) such that the most theoretically and clinically meaningful time scale is used. For example, constructs commonly proposed as mechanisms, such as alcohol craving, emotion regulation, social support, and self-efficacy (Boness &

Witkiewitz, 2023; Magill et al., 2020), are often measured months apart when testing mechanisms of change. These constructs change within and across days, however, demonstrating a mismatch between theory and measurement.

Shifts to more refined measurement time scales (e.g., moments and days) also align with how treatment providers delivering AUD interventions seek to target these mechanisms (e.g., facilitating mindfulness in the moment or increasing engagement in recovery supportive social activities on high-risk days). For example, Miranda Jr. et al. (2016) used an intensive longitudinal design and ecological momentary assessment (EMA) in a clinical trial of topiramate for alcohol use, whereby participants reported on the proposed mediator, alcohol craving, and outcome, alcohol use, several times per day throughout the treatment period. EMA was selected to measure craving and alcohol use due to the hypothesized mechanism of action of topiramate in blunting in-the-moment alcohol craving and theoretical and empirical research demonstrating craving as a momentary risk factor for alcohol use. Intensive longitudinal designs are useful, in that they can increase power, shorten study duration, lower the sample size needed to detect an effect, and reduce costs (Carpenter et al., 2020; Treloar Padovano & Miranda Jr., 2018). As with any approach, however, the benefits of intensive longitudinal designs should be considered alongside their appropriateness for specific populations (e.g., Markowski et al., 2021) and shortcomings such as participant burden (Trull & Ebner-Priemer, 2013).

Measuring etiological mechanisms

Treatments may be more effective for different individuals depending upon the specific mechanisms driving their substance use (Carroll & Kiluk, 2017; McCrady, 2017). This point aligns with broader efforts in AUD treatment research to advance precision medicine by matching specific treatments to individuals (Kranzler & McKay, 2012; Litten et al., 2012). Recently, Boness and Witkiewitz (2023) suggested that etiologic and maintenance mechanisms of AUD — the behaviors or processes that lead to AUD development and sustainment of AUD, respectively — may facilitate the advancement of precision medicine efforts in reducing drinking and supporting recovery from AUD. Specifically, linking the processes theorized to cause and maintain risky drinking (and AUD) with specific treatment mechanisms may inform who responds best to a specific treatment at a given time, which is analogous to how precision medicine is used in other fields (e.g., cancer treatment).

Using the Etiological, Theory-based, Ontogenetic, Hierarchical (ETOH) framework (Boness et al., 2021), Boness and Witkiewitz (2023) provided specific examples of linking etiological and maintenance mechanisms with treatment mechanisms. For example, an individual with AUD who has poor coping capacities (i.e., challenges with coping caused alcohol use [etiologic mechanism] and/or are driving alcohol use [maintenance mechanism]) may respond better to CBT that targets improvements in emotion-based coping

skills (treatment mechanism). This approach to mechanism research strongly aligns with Zilcha-Mano (2021), who suggested that every construct measured over time contains a trait-like component (i.e., baseline individual characteristic or etiological and maintenance mechanism) that may moderate the state-like component (e.g., mechanism that changes over the course of treatment). To measure the trait-like etiological and maintenance mechanism (i.e., pre-treatment tendency to use emotion-based coping skills across time) and state-like etiological mechanism (i.e., implementing emotion-based coping skills at a given time during treatment), we would need both a reliable trait- and state-based measure of emotion-based coping skills. One challenge to this approach is that etiologic and maintenance mechanisms for risky drinking (and AUD) may be additive or interacting with one another, and thus isolating specific mechanisms may not be sufficient.

Research design and methodology

Consideration of context for testing mechanisms

Formal testing of MOBC typically occurs in the context of larger treatment outcome studies, often as a secondary aim (Black & Chung, 2014; Huebner & Tonigan, 2007; Magill et al., 2020; Magill & Longabaugh, 2013). This approach is likely driven by multiple factors, including funding priorities. But it can be suboptimal for several reasons (Cuijpers et al., 2019; Kazdin & Nock, 2003). First, treatment outcome studies often focus primarily on evaluating pre- and post-treatment outcomes among groups (e.g., treatment versus control), which is inconsistent with the fine-grained longitudinal assessment required to adequately capture MOBC (Black & Chung, 2014). According to Witkiewitz et al. (2022), longitudinal intensive data collection that can evaluate the extended temporal patterning of behavior–environment associations (i.e., people's behavior in context over time) is needed, and such designs may be inconsistent with the goals of traditional treatment outcome studies that tend to employ longitudinal panel designs with monthly (or fewer) assessments.

Need for greater specificity

The use of an experimental design, specifically, random assignment to an intervention, is a criterion for establishing a treatment mechanism (Hill, 1965; Kazdin & Nock, 2003), but it is not sufficient (Kazdin & Nock, 2003; Longabaugh, 2007; Magill & Longabaugh, 2013). Common behavioral interventions for treating AUD have many behavior change techniques (BCTs), or components, that are packaged together to produce change. This packaging makes it difficult to pinpoint the specific active ingredients of the specific intervention, resulting in a "black box" of how these interventions work (Huibers et al., 2020; Longabaugh, 2007; Magill & Longabaugh, 2013; Moos & Finney, 1983). Accordingly, AUD researchers have proposed that

clarifying and isolating the active ingredients is needed to look into the "black box" (Longabaugh, 2007, Magill & Longabaugh, 2013). Beyond difficulty in isolating active ingredients, even more concerning is that recent work suggests that targeting multiple BCTs may weaken effects on mechanisms and treatment outcomes. Specifically, Baker et al. (2021) demonstrated that burden (i.e., fatigue or distraction resulting from administration of multiple BCTs) and overlapping mechanisms (i.e., reduced effects on a mechanism due to multiple BCTs that target the same mechanism) actually weakened a smoking cessation intervention. In addition to isolating active ingredients of behavior change, other researchers have advocated for assessing interactions between BCTs and/or the specific sequencing of BCTs (Lorenzo-Luaces, 2023; Watkins et al., 2023). Regardless of whether a study examines single or interacting BCTs, mechanism research of behavioral interventions with health providers should account for therapeutic alliance, a factor outside the intervention itself shown to result in alcohol use behavior change within alcohol use treatment (Connors et al., 2016; Kazdin & Nock, 2003), as well as other potential common treatment factors (e.g., empathy and genuineness; Wampold, 2015).

Consideration of dose

Treatment outcome studies are typically more concerned with fidelity (or adherence) to the overall treatment rather than the fidelity of each specific BCT component. As a result, the "dose" of a given treatment component may be insufficient for altering the mechanism of interest. Dose may also be challenging to measure and may differ between and within individuals. Given dose is an important requirement for testing mechanisms (Kazdin, 2007), it is critical for researchers to specify how and when dose will be assessed. Gradient, another requirement for testing mechanisms, requires altering the dose of the BCT to determine whether a stronger dose leads to greater engagement of a mechanism and, in turn, greater change in the outcome of interest (Hill, 1965; Kazdin & Nock, 2003). Manipulating the BCT dose is not only important to demonstrate stronger engagement of a mechanism but also to demonstrate that null effects between a BCT and candidate mechanisms are not the result of an insufficient BCT dose (Magill & Longabaugh, 2013; Morgenstern & Longabaugh, 2000). Importantly, there may or may not be a meaningful dose response effect of a treatment under study depending on its neuropharmacology (for pharmacotherapy trials) and saturation/boredom (for behavioral treatments). The neuropharmacology of the investigational drug of interest and necessary dose of behavioral treatment, as well as their theoretical effects on a mechanism, should guide whether increasing the dose is appropriate.

Experimental design

In addition to BCT randomization, an experimental paradigm of the mechanism evaluated in a sample for whom an intervention is

intended also facilitates building evidence toward a treatment mechanism (Witkiewitz et al., 2022). Although uncommon in behavioral interventions for AUD, the use of experimental paradigms is common in medication development research. For example, Miranda Jr. et al. (2020) conducted a randomized clinical trial of varenicline on alcohol craving using a cue reactivity paradigm. A human laboratory cue reactivity paradigm was selected to experimentally test the candidate mechanism of varenicline (i.e., reductions in craving) in a manner that was time-limited. Using experimental paradigms to test engagement of a mechanism may help expedite mechanism research and facilitate causal conclusions regarding the relationship of a mechanism with a treatment outcome. Reliable and valid experimental tasks exist for measuring proposed mechanisms of AUD treatment including craving (Reynolds & Monti, 2013), delay discounting (Koffarnus & Bickel, 2014), emotion regulation (Kanske et al., 2011), and inhibitory control (Logan et al., 1997). Employing such a design would facilitate a strong test of signal for engagement of a mechanism with internal validity.

Statistical methods

The use of robust statistical methods is critical for testing MOBC. Yet the MOBC literature faces many statistical shortcomings and challenges. Prominent issues include statistical power, outcome distributions, and approaches to testing mechanisms.

Power

Because treatment outcome studies are primarily powered to test pre- and post-treatment outcomes, there may be insufficient power to adequately test MOBC (Magill et al., 2020; Magill & Longabaugh, 2013; Meisel et al., 2022). Thus, adequately powered tests of treatment mechanisms are critical.

Outcome distributions

Alcohol use outcomes are often non-normally distributed (typically bimodal, zero-inflated, and/or count outcomes), and many researchers either assume normal distributions or fail to consider distributional assumptions in conducting analyses (Witkiewitz et al., 2015). Failing to adequately model the distributions of interest can introduce bias into the estimation of outcomes and reduce power to detect effects of interest.

Moving beyond simple mediation models

The historical conflation of mediators and mechanisms in the MOBC literature has resulted in the use of insufficient statistical models for establishing MOBC. Although statistical mediation is a necessary condition, it is not sufficient for elucidating MOBC (Boness & Witkiewitz, 2023; Huebner & Tonigan, 2007; Kazdin & Nock, 2003; Longabaugh & Magill, 2011; Witkiewitz et al., 2022). Witkiewitz et al. (2022) recommend moving beyond simple mediation models and instead using other quantitative approaches to test MOBC more appropriately. For example, time-varying effect models (Hallgren et al., 2018; Meisel et al., 2021), mixture modeling approaches (Vest et al., 2020; Witkiewitz et al., 2018), and models that better account for individual differences in change trajectories, such as person-specific machine learning models (Soyster et al., 2022), predicted individual treatment effect models (Kuhlemeier et al., 2021), and likely responder analyses (Laska et al., 2020). Relative to longitudinal mediational models, these analytic approaches can help inform what mechanisms operate for what person and guide our knowledge of the timing of mechanisms and outcomes.

A path forward: A proposed methodological framework for testing mechanisms

A methodological framework that tests mechanisms rather than treatment mediators needs to address the criteria for assessing mechanisms (Hill, 1965; Kazdin & Nock, 2003). Figure 1 details how the steps involved in this proposed framework, described below, satisfy these criteria for establishing evidence for a mechanism.

Step 0: Articulate theory

Testing an MOBC first requires articulating a plausible and testable theory that is comprehensive and specific to the larger causal chain of processes, including contextual and temporal processes, that result in a certain treatment outcome. The Theoretical Domains Framework (see Cane et al., 2012; Michie et al., 2005) and ontology-based modeling system for behavior change theories (Hale et al., 2020; West et al., 2019) can be referenced for prior theoretical development work in behavior change theories. Additionally, the National Institutes of Health Science of Behavior Change Common Fund program was a strategic initiative to support researchers in theory development and testing MOBC (Nielsen et al., 2018). This program advocates for a translational approach to mechanisms research, whereby basic science and preclinical models inform candidate mechanisms and theory development for testing treatment mechanisms (Nielsen et al., 2018). Resources for measurement and theory development are available at https://commonfund.nih.gov/behaviorchange. Adopting these frameworks in studies of mechanisms will facilitate more consistent terminology for theories and mechanisms. In turn, this may aid meta-analytic efforts and the integration of mechanism research across disciplines and the translational spectrum (Meisel et al., 2022; Nielsen et al., 2018).

Step 1: Baseline assessment of mechanism, outcome, and etiological mechanism

Mechanisms should be tested in the population for whom an intervention is ultimately intended to treat. Therefore, sample selection should be guided by the intended treatment sample (e.g., clinical populations and individuals recruited from the emergency department for engaging in risky alcohol use). Prior to randomizing participants to condition, assess the putative treatment mechanism, focal outcome(s), and etiological mechanism (i.e., behaviors or processes that lead to the development and sustainment of AUD) using reliable and valid measures. The time frame (e.g., moment, day, and week) for measuring the mechanism and outcome(s) should be guided by theory and clinical relevance. If theoretically appropriate, we advocate for the use of intensive longitudinal designs (e.g., daily diary and EMA) to measure candidate mechanisms, common factors (e.g., therapeutic alliance), and relevant treatment outcomes in conjunction with experimental designs (further detail in Step 3). These intensive longitudinal assessments should begin immediately after the baseline session to adequately account for pre-treatment changes in the mechanism(s) and outcome(s) (Noyes et al., 2018; Stasiewicz et al., 2019) and continue throughout the duration of the study whenever feasible and appropriate.

To identify a mechanism, variables need to be assessed using reliable and valid measures (Mackinnon et al., 2007). Threats to validity or reliability can significantly undermine the opportunity for a study to meaningfully contribute to the evidence based on treatment mechanisms. Mediators with poor reliability attenuate the *b* path and overestimate the *c* path in a mediational chain (see Figure 2), which in turn leads to the indirect effect being underestimated (Gonzalez & MacKinnon, 2021). Conversely, using reliable measures of a theoretical mediator enhances statistical power without increasing sample size (Fritz et al., 2015).

In addition to maximizing the ability to detect a mechanism, baseline assessment of the treatment mechanism, etiological mechanism, and treatment outcome(s) is necessary to establish temporal precedence (mechanisms criteria 4; Loh & Ren, 2023). Moreover, a baseline assessment of the probable etiological mechanism(s) for a given person's risky drinking may facilitate the advancement of precision medicine efforts (Boness & Witkiewitz, 2023; McCrady, 2017).

Reliable and valid assessment of the etiological mechanism prior to randomization to condition (Step 2) places a focus on precision medicine at study onset. A better understanding of whether specific BCTs engage a mechanism for specific people and whether mechanisms predict treatment outcomes for specific people is essential to advance precision medicine efforts (Boness & Witkiewitz, 2023, McCrady, 2017).

Step 2: Random assignment to condition

Ideally, studies would randomly assign participants to at least four conditions: (1) a control condition (e.g., placebo or attention control or minimal treatment control with no active BCTs that are aligned with purported mechanisms), (2) the BCT of interest at a theoretically appropriate dose, (3) the BCT at a different dose (e.g., often a greater dose of the BCT) than of condition 2, and (4) a BCT theoretically unrelated to the mechanism of interest. To adequately capture the dose, researchers should measure the amount of a BCT or medication dosage as well as engagement and uptake of the BCT (e.g., BCT skill use and medication compliance).

Testing a specific BCT, rather than an entire multicomponent treatment, may improve specificity of the *a* path by informing which specific treatment ingredient engages a mechanism. This approach allows for testing micro-interventions to assess engagement in a theoretical mechanism (Nielsen et al., 2018; Smith Slep et al., 2023). In addition to addressing the "black box" issue, there are several other potential benefits of testing BCTs. First, a shift from testing entire treatments to specific BCTs would more strongly align pharmacotherapy and behavioral treatments mechanism research. When testing for a signal for novel medication targets for AUD, a single medication is tested and its effects on candidate mechanisms examined (e.g., Miranda Jr. et al., 2020). In addition to satisfying the condition of specificity for a mechanism, randomly assigning individuals to conditions and multiple doses whenever appropriate or clinically indicated satisfies the mechanism criteria of experimental design and gradient, respectively. The dose represents the amount of a BCT provided paired with the engagement and uptake of the BCT. For example, in addition to medication dose (e.g., 25 vs 50 mg), assessing an individual's medication compliance is also a central component in evaluating their true dose. Accordingly, assessment of BCT skill uptake and medication adherence is critical to being able to establish a dose–response relationship.

Manipulating the dose of the BCT can inform the dose needed to successfully engage a treatment mechanism. Moving from testing multicomponent interventions, which can take weeks to months to complete (e.g., 12 sessions of CBT), to BCTs, that can be completed in minutes to hours, will increase the efficiency of testing treatment mechanisms. Further, developing an evidence base for specific BCTs and their mechanisms may help advance AUD treatments in several ways. First, it would help streamline AUD interventions by informing which BCTs (i.e., intervention ingredients) are necessary and which are unnecessary to actively engage a treatment mechanism of interest. This would facilitate efforts to effectively implement and disseminate evidence-based treatments for AUD (Magill et al., 2023). Second, knowledge of the BCTs that engage specific mechanisms may aid the development of interventions consisting of only a few BCTs such as single-session interventions, brief interventions, and mobile health interventions for AUD (Schleider & Beidas, 2022; Schleider & Weisz, 2017; Spohrer et al., 2021).

Step 3: Engagement of mechanism

Assessing the impact on mechanisms with experimental paradigms can help inform our understanding of mechanisms. Studies of novel

medication targets often use experimental paradigms (e.g., cue reactivity paradigm; Miranda Jr. et al., 2020, Rohsenow et al., 1991) to evaluate whether a medication engages a theoretically informed mechanism of interest. One benefit of laboratory-based paradigms is the ability to test the *a* path with strong internal validity. Intensive longitudinal methods also provide important benefits in building evidence toward a mechanism. They provide a test of the *a* path with strong external validity (Treloar Padovano & Miranda Jr., 2018), facilitate separating trait-like from state-like variability in the putative mechanism (Zilcha-Mano, 2021), and provide temporal precedence such that BCTs can prospectively predict the intensive longitudinal measure of your mechanism, which in turn, can predict your outcome.

Having an experimental paradigm, whenever possible and applicable, as well as an intensive longitudinal measure of a candidate mechanism helps build initial evidence toward the mechanism criteria of consistency. Consistency refers to the mechanism replicating across studies. Although no single study can provide sufficient evidence for consistency, replicating findings across methods within a single study provides initial evidence for consistency.

The use of an experimental paradigm coupled with an intensive longitudinal assessment of the mechanism provides both an internally and externally valid test of the mechanism, respectively. Further, the use of multiple methods enhances falsifiability of a mechanism by being able to demonstrate that a mechanism is supported or not supported across methods. Of note, experimental paradigms exist for many of the constructs forwarded as MOBC for AUD (e.g., see Boness & Witkiewitz, 2023 for a list of mechanisms). However, researchers should not be compelled to use an experimental paradigm in cases where one does not exist for a construct.

Step 4: Assess change in outcome

Examine whether the mechanism, assessed using an experimental paradigm and intensive longitudinal assessment whenever possible, prospectively predicts your outcome(s) of interest. The timeframe for assessing the outcome should be guided by theory and existing research to capture sufficient variability in the outcome of interest (Hopwood et al., 2021). Adhering to Steps 1–3 will position a study to examine the *b* path across methods (i.e., experimental paradigm and intensive longitudinal measure of a candidate mechanism predicting the treatment outcome) with temporal precedence, meeting the strong association and temporal relation mechanism criteria by testing the prospective association between the mediator and treatment outcome(s) (*b* path) in Step 4. Again, since this framework advocates for using intensive longitudinal designs of the outcome of interest, the test of the *b* path of a mechanism would have greater statistical power. As with Step 3, although no single study can meet the criteria of consistency, support for the *b* path across methods would provide initial evidence of consistency.

EXAMPLES

We offer two examples of the proposed methodological framework. Both focus on craving, a theorized etiologic and maintenance mechanism in risky drinking and AUD (Boness et al., 2021), as a MOBC in a pharmacologic treatment (naltrexone) and a behavioral treatment (urge surfing from Mindfulness-Based Relapse Prevention [MBRP]).

Step 0: Theoretical underpinning

Naltrexone, an opiate receptor antagonist, is a medication that reduces heavy alcohol use in adults and adolescents (Maisel et al., 2013; Miranda et al., 2014). It is hypothesized to work by blunting dopaminergic transmission in mesolimbic pathways (Benjamin et al., 1993), thereby attenuating craving. Meta-analyses in laboratory-based and natural environment studies demonstrate naltrexone reduces alcohol craving (Hendershot et al., 2017; Maisel et al., 2013; Ray, Green, et al., 2019), which is associated with reductions in alcohol use (Witteman et al., 2015).

Urge surfing is a skill included in evidence-based treatments such as MBRP (MBRP; Marlatt & Donovan, 2005). It involves teaching a client to nonjudgmentally focus on, observe, and accept substance-related craving in the moment (Bowen & Marlatt, 2009). Clients visualize their craving as an ocean wave and use mindful awareness of their breath to "ride out" the wave. Urge surfing, as brief as a single 20-minute session, is theorized to reduce alcohol and other substance use among adolescents and adults through reductions in craving (Bowen & Marlatt, 2009; Harris et al., 2016; Marlatt & Kristeller, 1999).

Step 1: Complete a baseline assessment of mechanism, outcome, and etiological mechanism

Table 2 includes measures to examine craving as a mechanism of naltrexone and urge surfing based on their psychometric properties. In addition to trait-based measures of the mechanism, etiological mechanism, and outcomes (e.g., alcohol-related problems and meaning in life), administration of EMA measures of these constructs would also start during the baseline assessment.

Step 2: Random assignment to condition

Within the proposed framework for studying naltrexone, individuals would be randomly assigned to one of the following four conditions: (1) placebo (control), (2) naltrexone target dose of 50mg/day (BCT dose 1), (3) naltrexone target dose of 100mg/day (BCT dose 2), and (4) disulfiram 250mg (BCT unrelated to craving). Disulfiram, which inhibits the liver enzyme aldehyde dehydrogenase (Jorgensen et al., 2011), is associated with improved abstinence rates and

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TABLE 2 Measures for worked examples.

Target	Measure	Psychometrics	Method and Time-Scale	Administration period		
				Baseline	Immediately Post BCT Administration	End of Study
Naltrexone (BCT Medication Worked Example)	Medication Event Monitoring System	El Alili et al. (2016)	Electronic bottle cap measuring data/time bottle opened			↑
	"What time did you take your study capsule?" "How many study capsules did you take?"	El Alili et al. (2016)	EMA; current day			↑
Urge Surfing (BCT Behavioral Worked Example)	Mindfulness-Based Relapse Prevention Adherence and Competence Scale[a]	Lahtinen and Salmivalli (2020)	EMA; current day	↑———————	———————	———————↑
	"How many minutes did you practice urge surfing today?"	Lahtinen and Salmivalli (2020)				
Craving (Treatment Mechanism and Etiologic and Maintenance Mechanism)	Alcohol Urge Questionnaire	Drummond and Phillips (2002), MacKillop (2006)	Self-Report; right now	X		
	Alcohol Cue-Reactivity Paradigms	Reynolds and Monti (2013), Stritzke et al. (2004)	Experimental paradigm; current moment	X	X	
	How strong is your urge to drink alcohol right now?	Boyett et al. (2021)	EMA; current moment	↑———————	———————	———————↑
Alcohol Use (Outcome)	Timeline Follow Back	Sobell and Sobell (1992), Hernandez-Vallant et al. (2023), Carey (1997)	Interview or Online Administration; past month	X		X
	Ounces consumed and alcohol type	Freeman et al. (2022), Kaplan and Koffarnus (2019)	EMA; past day	↑———————	———————	———————↑
Alcohol-Related Problems (Outcome)	Rutgers Alcohol Problems Index	Haeny et al. (2018), Dick et al. (2011), Earleywine et al. (2008), Shono et al. (2018)	Self-Report; past month	X		X
	Daily assessment of alcohol consequences	Lee et al. (2017), Merrill et al. (2021), Merrill et al. (2018)	EMA; past day	↑———————	———————	———————↑
Meaning in Life (Outcome)	Meaning in Life Questionnaire	Steger et al. (2006), Schulenberg et al. (2011)	Self-Report; right now	X		X
	Meaning in Life	Heintzelman and Mohideen (2022)	EMA; past day	↑———————	———————	———————↑

Note: Arrows reflect continuous measurement from one period to the next.

[a]A measure of BCT fidelity should be included for all behavioral interventions delivered by a health provider, as poor intervention fidelity may alter the dose of BCT that a participant receives.

number of drinking days but is not hypothesized to reduce craving (Boness & Witkiewitz, 2023).

For the urge surfing example, individuals would be randomly assigned to the following four conditions: (1) sham mindfulness meditation matching the urge surfing exercise in duration and general structure (e.g., Ruscio et al., 2016), (2) 10-minute urge surfing exercise, (3) 20-minute urge surfing exercise, and (4) 20-minute brief normative feedback intervention. Brief normative feedback interventions have been shown to reduce alcohol use, although their theoretical mechanisms of action do not include craving (Neighbors et al., 2016; Pedersen et al., 2017).

Step 3: Engagement of mechanism

After individuals in all conditions reach their target dose (naltrexone) or training period (urge surfing), they would be scheduled for a session assessing the mechanism of action, craving. Individuals across all conditions would complete an alcohol cue reactivity paradigm. This would facilitate examining whether the condition was associated with craving (a-path in Figure 2) as assessed using a cue-reactivity paradigm (experimental paradigm). Additionally, the condition could predict craving in the natural environment (using EMA) since craving captured by EMA would be measured beginning at the start of the study. Using EMA over a duration of 3 weeks or less should be sufficient to detect changes given both medications are relatively fast-acting.

Step 4: Assess change in outcome

Lastly, an end-of-study session would include the assessments listed in Table 2. Of note, as with the a-path, changes in the outcome of interest could be tested across multiple timelines. Craving assessed from the cue-reactivity paradigm in the lab (Step 3) could predict treatment outcomes measured at the end of study visit as well as treatment outcomes measured using EMA. Additionally, craving assessed using EMA could predict treatment outcomes measured at the end of study visit as well as treatment outcomes assessed using EMA.

CONCLUSIONS

Testing MOBC is complex but key to AUD intervention development. In this critical review, we sought to facilitate a shift to testing treatment mechanisms by forwarding an etiologically informed precision medicine approach to studying behavior change. This framework and multistep approach meets all the mechanism criteria set forth by others (Hill, 1965; Kazdin & Nock, 2003) and aims to advance future efforts to elucidate how treatments work. This framework also helps align AUD mechanism research with precision medicine efforts (Boness & Witkiewitz, 2023), current theories of etiologic AUD

mechanisms (Boness et al., 2021), and cross-disciplinary approaches to testing mechanisms (Cane et al., 2012; Nielsen et al., 2018; West et al., 2019). Considering the complexity of AUD treatment mechanism research, our major objective is to help advance what we know about how and for whom interventions work. This framework is not intended to resolve all issues associated with the exploration of mechanisms in AUD research.

There is no question that advancing our understanding of AUD treatments and improving clinical care for people who struggle to reduce their alcohol use requires clinical scientists to contend with several critical challenges when it comes to mechanism research. We must work to refine the relevant time scales for capturing putative mechanisms and focal outcomes. Theoretical models would benefit from greater specificity regarding the timing of change processes in their frameworks. Precision in the timing of a change processes is essential to rigorous and falsifiable research (Hopwood et al., 2021). Without clearer articulations of timing, it will remain difficult to have falsifiable theories of behavior change, as null findings may be due to improper timing of assessments. Additionally, even if assessments occur at theoretically appropriate time scales, reliance on measures with poor reliability, validity, or that fail to sufficiently capture change will weaken tests of mechanisms (Gonzalez & MacKinnon, 2021). Continued efforts to establish psychometrically strong measures for use in mechanisms studies, including EMA measures, will be important (e.g., Boness et al., 2024).

We must also consider that behavior change may result not from a single BCT but rather from interactions among different BCTs, synergy between different BCTs, or as the result of ordering of specific BCTs (Lorenzo-Luaces, 2023; Watkins et al., 2023). Although we advocate for the isolation of BCTs within the proposed framework as a starting place for looking into the "black box" and addressing other limitations of treatment mechanism research (Table 1), those advancing arguments for the importance of considering interactions and sequential effects of BCTs may argue this is too reductionistic. We are sympathetic to this concern and look forward to future treatment research that considers the isolation versus combination of BCTs. One possibility for future research is to use methods such as Sequential Multiple Assignment Randomized Trial (SMART) and Multiphase Optimization Strategy (MOST) to identify specific BCTs as well as any necessary ordering of BCTs and then to examine their corresponding mechanisms within our proposed framework (Collins et al., 2007). Indeed, tearing apart these complex interactions will be an important avenue for future research.

Our understanding of MOBC must also consider important and intersecting identities and community-level factors and their roles in AUD etiology and recovery (Hennessy et al., 2019; Witkiewitz et al., 2022). Integration of intersectionality and community-level factors into theoretical models of AUD recovery mechanisms as well as developing statistical methodologies that can account for multiple moderators (i.e., how do we examine a mechanistic pathway that may include factors such as age, biological sex, racism, and alcohol outlets as moderators, simultaneously) will be important to create ecologically valid and inclusive AUD mechanism research.

Despite these and other remaining challenges in AUD mechanism research, we believe identifying mechanisms of AUD and identifying for whom those mechanisms operate remains an important research pursuit. As the landscape of available treatment options continues to grow and expand to new platforms (e.g., social media and mobile health), we need to advance our understanding of how and for whom different interventions work. Identifying mechanisms that promote behavior change, and the BCTs that elicit change in those mechanisms, may yield important information that can improve recovery efforts for AUD. Most individuals who require treatment for AUD still never receive formal treatment, and the mechanisms of natural recovery remain unclear (Tucker et al., 2020). Understanding the MOBC may help reduce interventions to their core ingredients and facilitate the implementation of evidence-based treatments in the community (Magill et al., 2023). To advance these goals, we advocate for the resources necessary to support this type of research (e.g., increased research funding and supports to facilitate team science).

CONFLICT OF INTEREST STATEMENT

The authors deny any conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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