11-15-2021

Relief and Reward Drinking Across Time in Community and Treatment-Seeking Samples

Julia E. Swan
University of New Mexico - Main Campus

Julia E. Swan, B.A.
Candidate

Psychology
Department

This thesis is approved, and is acceptable form and quality for publication:

Approved by the Thesis Committee:

Katie Witkiewitz, Ph.D., Chairperson

Eric Claus, Ph.D.

Nathan Pentkowski, Ph.D.

RELIEF AND REWARD DRINKING ACROSS TIME IN COMMUNITY AND TREATMENT-SEEKING SAMPLES

BY

JULIA E. SWAN

B.A., UNIVERSITY OF MICHIGAN, 2017

THESIS

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Master of Science

Psychology

The University of New Mexico

Albuquerque, New Mexico

December 2021

RELIEF AND REWARD DRINKING ACROSS TIME IN COMMUNITY AND TREATMENT-SEEKING SAMPLES

by

Julia E. Swan

B.A., University of Michigan, 2017

M.S., University of New Mexico

ABSTRACT

Classifying people with alcohol use disorder into homogenous groups based on observed characteristics (i.e., phenotypes) could match individuals to specific treatments. The reward-relief phenotype classifies individuals based on whether they drink to enhance rewarding experiences and/or to relieve negative states. The current study is a secondary data analysis of a community sample of non-treatment seeking heavy drinkers (n = 189) and two randomized clinical trial samples of individuals with alcohol use disorder (n = 1726, 1383) that aimed to determine if the reward-relief phenotype is identified across samples, is stable over time, and predicts long-term alcohol consumption and consequences. We found the four-profile reward-relief phenotype replicated, and the baseline phenotype predicted drinking outcomes in all samples. However, only in the non-treatment-seeking sample was the phenotype stable over time. Though further research is warranted, there is evidence that group membership by the reward-relief drinking phenotype could predict drinking outcomes over time.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Introduction

In the United States, almost fifteen million adults meet criteria for alcohol use disorder every year, and more than thirty million adults binge drink every month (Centers for Disease Control and Prevention, 2018; Substance Abuse and Mental Health Services Administration (SAMHSA), 2018). Consequences of these patterns of alcohol use include loss of human life through sudden causes such as acute alcohol intoxication, driving fatalities, and fall injuries, and chronic causes such as alcohol-related liver disease, certain cancers, and hypertension (Centers for Disease Control and Prevention, 2013). In 2010, the estimated economic consequences of these patterns of alcohol use to the government and taxpayers include $249 billion a year for health care, lost productivity, and legal system expenses (Sacks et al., 2015).

Despite these consequences, treatments are underutilized. Only 25% of people with alcohol use disorder seek treatment (Dawson et al., 2005), including empirically supported psychosocial therapies and pharmacological treatments (e.g., Akbar, Egli, Cho, Song, & Noronha, 2018; Kelly, 2017; Ray et al., 2019). Even when these treatments are implemented (Young et al., 2018), they are not always as efficacious as expected when compared to control or placebo conditions with small to moderate effect sizes for the best empirically supported psychosocial and pharmacological treatments (Maisel et al., 2013; Ray et al., 2019).

A possible reason for this limited efficacy may be because alcohol use disorder is heterogeneous in its neurobiological development, symptomology, and presentation. For example, using the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (American Psychiatric Association, 2013; Lane & Sher, 2015; Litten et al., 2015; Tawa et

al., 2016) there are 2,048 combinations of symptoms that could lead to an alcohol use disorder diagnosis. By classifying (i.e., subtyping) people with alcohol use disorder, more homogenous groups may have better outcomes by targeting a specific mechanism of action, observable characteristic (i.e., phenotype), or genotype that reinforces alcohol use. Through classification, these treatments could be applied to a specific set of individuals who are most likely to benefit from a specific treatment (Litten et al., 2015; Mann et al., 2018).

Classification Models of Alcohol Use Disorder

Classification efforts for those with alcohol use disorder formally began in the 1960s with Jellinek's "species" of alcohol use disorder as determined from a survey of people who attended Alcoholics Anonymous (Jellinek, 1960). While Jellinek delineated five subtypes, only two of those would fall within our current definition of alcohol use disorder (Jellinek, 1960). Gamma, the most common subtype, emphasized a person's loss of control once they began to drink alcohol but the ability to abstain otherwise. The delta subtype had similar characteristics to gamma, but the loss of control facet was instead replaced by an inability to abstain from drinking. Jellinek did not hypothesize the stability of these subtypes or possible treatment implications (Jellinek, 1960; Kelly, 2019). While this was a step in the right direction, these subtypes have only been implemented in a limited fashion or in conjunction with later phenotypes (Epstein et al., 1995; Leggio et al., 2009).

Two other classification systems that have previously been used in clinical trials are Cloninger and colleagues' Type I and Type II (Cloninger et al., 1981) and Babor and colleagues' Type A and Type B (Babor et al., 1992). Those who fall under Cloninger's Type I subtype develop alcohol use disorder later in life and use alcohol for self-medicating purposes. Those under Type II develop alcohol use disorder earlier in life and use alcohol for

rewarding reasons. Cloninger's subtypes have received mixed empirical support with some studies fully replicating the subtypes (Sigvardsson et al., 1996), partially replicating (Glenn & Nixon, 1996; Yoshino et al., 1994), and others failing to replicate or finding that age of onset eclipses all other features of the subtypes (Irwin et al., 1990; Sannibale & Hall, 1998; Von Knorring et al., 1985).

Cloninger developed his subtypes based on personality theory, but he later hypothesized that people in Type I would have dopaminergic dysfunction and those in Type II would have serotonergic dysfunction (Cloninger, 1987, 1995; Cloninger et al., 1981). In more recent years, these theoretical dysfunctions have been upheld in several imaging studies with Type I having differences in dopaminergic firing in the striatum compared to controls and Type II showing differences in the density of serotonin transporters in the hypothalamus (Storvik et al., 2008; Tiihonen et al., 1995; Tupala et al., 2003).

Babor and colleagues created a similar binary model to Cloninger's defined as Type A and B (Babor et al., 1992). Type A was characterized by alcohol problems later in life, fewer developmental risk factors, less severe symptoms and consequences, and less psychopathology generally. Type B was characterized by the opposing characteristics, alcohol problems earlier, more developmental risk factors, more severe symptoms and consequences, and comorbid disorders and substance use. Babor and Cloninger's types only overlap in probable age of onset, but the types are often combined as Cloninger I/Babor A and Cloninger 2/Babor B (Leggio et al., 2009). However, unlike Cloninger's, Babor's subtypes have been replicated and supported in multiple studies beyond age of onset (Epstein et al., 2002; Litt et al., 1992; Ribeiro et al., 2015; Schuckit et al., 1995). This support may be the result of Babor's subtype development from a broad range of domains through cluster

analysis of treatment-seeking patients with alcohol dependence whereas the Cloninger's subtypes were based only on personality theory with adopted sons of parents with alcohol use disorder (Babor et al., 1992; Cloninger et al., 1981; Leggio et al., 2009). A limited number of clinical trials have examined drinking outcomes based on Babor's subtypes (Bogenschutz et al., 2009; Pettinati et al., 2004), and they have found that those with Type A had better outcomes on naltrexone and sertraline, but those defined as Type B had no significant differences in drinking outcomes regardless of medication treatment assignment. While these models have some support, there is also concern with both of these models for the clinical utility of any binary model in such a complex disorder (Epstein et al., 2002).

Additional subtypes have been created in more recent years like Lesch and Walter's four subtypes (Type I-IV; Lesch & Walter, 1996). The characteristics of these subtypes consist of reasons for drinking, family history, childhood risk factors, interpersonal changes, and somatic concerns. Lesch's subtypes have had mixed support from genetic evidence (Hillemacher & Bleich, 2008; Samochowiec et al., 2008) and have failed to replicate in other datasets (Walter et al., 2006). Treatments based on Lesch's types have been proposed (Lesch & Walter, 1996; Schlaff et al., 2011), but they have not been tested prospectively in any clinical trials (Hesselbrock & Hesselbrock, 2006; Schlaff et al., 2011). However, two studies have examined post-hoc drinking and treatment outcomes based on Lesch's subtypes. One outpatient study found that patients classified as Lesch's Type IV had lower levels of abstinence and utilized clinical resources less than other patients over a three-month follow-up (Pombo et al., 2015). Another study found that female patients enrolled in inpatient treatment centers classified as Type I were more likely to be readmitted to the hospital for treatment in the 24 months following treatment, and those classified as Type II were less

likely to be readmitted to the hospital than all other Lesch's subtypes (Weinland et al., 2017). Both studies found support for only portions of the phenotype, and more research is needed. However, these subtypes appear to be a step in the right direction with the phenotype having possible implications in clinical settings, being characterized by more than two groups, and being characterized by some historical factors (e.g., family history) and dynamic or changing factors (e.g., somatic concerns).

Finally, Moss and colleagues found five clusters of people with alcohol dependence using latent class analysis, including the young adult subtype, functional subtype, intermediate familial subtype, young antisocial subtype, and chronic severe subtype (Moss et al., 2007). Moss's clusters were recently proposed, and the only additional articles supporting the clusters utilize the original dataset and were written by the original authors (Moss et al., 2008, 2010).

Overall, these subtypes have not found ample support or been well-utilized in clinical trials or settings. Jellinek and Cloninger's models both brought to the forefront important aspects of alcohol use disorder including loss of control, reasons for alcohol use, environmental influence, and genetic factors. However, as phenotypes, they were not well-replicated or utilized in treatment settings. Babor's model has more empirical support, including replication of the phenotypes in independent samples and validation of the phenotypes by examining medication outcomes by subtype. Lesch's model has also found some support when examining treatment and drinking outcomes by subtype; however, it has not been replicated and has only found partial support for the phenotype in any individual study. Moss's model has not been studied enough to draw any conclusions.

There are a few additional strengths and limitations of each of the proposed phenotypes. Strengths included the small number of subtypes allowing for practical use of the phenotype, and all the models consider multiple aspects of the disorder as well, although Cloninger's model can be reduced to age of onset. However, there are also several limitations of these models. First, most of the models were developed with historical or behavioral human factors in mind and have not considered biological substrates of alcohol use disorder. Additionally, the models have only been tested in limited clinical samples with a narrow range of alcohol use disorder severity, and most of these subtypes have not been utilized to determine treatment efficacy by subtype.

Classification Models based on Neurotransmitter Dysfunction

Changes in dopamine and opioids. Previous research based on animal models, molecular findings, and human neuroimaging has elucidated possible avenues for the classification of people with alcohol use disorder beyond historical and psychological factors. Specific molecular dysfunctions prior to substance use or neuroadaptations after substance use have been identified, including dysfunctions in neurotransmitters such as dopamine, opioids, GABA, glutamate, and serotonin (Banerjee, 2014; Spanagel & Weiss, 1999; Spanagel & Zieglglnsberger, 1997; Verheul et al., 1999). One of the primary pathways that is discussed in substance use disorder acquisition is the mesolimbic pathway of dopamine neurons, which is thought to play a major role in reinforcement and reward processes (Spanagel & Weiss, 1999). One theory based on the dopamine system in animal models is the incentive-sensitization theory (Robinson & Berridge, 1993). This theory posits that repeated drug use creates neuroadaptations in the brain that hypersensitize the dopamine system producing compulsive drug use. The "liking" of the drug, or the euphoric effects,

dominate the initial exposures to the drug, while repeated drug use over time increases the conditioned craving of the drug, called "wanting". The incentive-sensitization theory may explain why cues for substances may not be extinguished for years because of previous neuroadaptations. Neuroimaging studies in humans have found that during exposure to alcohol cues those with alcohol use disorder had greater activation in the insula, ventral striatum, posterior cingulate cortex, precuneus, and superior temporal gyrus compared to controls (Ihssen et al., 2011; Schacht et al., 2013). Several of these areas, like the ventral striatum and insula, are hypothesized to be part of the reward pathways that may reinforce drug use (Koob & Volkow, 2016). This theory also posits that chronic alcohol and substance use can lead to reduced dopamine transmission and a decrease in the release of endogenous opioids (Koob & Volkow, 2016). Further, dysfunction in the reward system can lead to greater negative affect, including irritability and dysphoria (Koob & Volkow, 2010, 2016).

This theory also emphasizes that pharmacological therapies can be used to treat the effects of sensitization to addictive substances. Research in animal models has found that blocking opioid receptors reduced voluntary alcohol consumption, which supported the development of naltrexone as a treatment for alcohol use disorder (Herz, 1997; Mann et al., 2013). Naltrexone is an opioid receptor antagonist and FDA-approved pharmacological treatment for alcohol use disorder. It is thought to function by blocking μ-opioid receptors on GABA interneurons in the ventral tegmental area and allowing these neurons to release GABA to $GABA_B$ receptors on dopamine neurons, ultimately inhibiting dopamine firing (Ray et al., 2012; Verheul et al., 1999). Another medication, nalmefene, was approved in the European Union for the reduction of alcohol use (Mann et al., 2016). Like naltrexone, it functions as an opioid receptor antagonist for μ-opioid receptors and δ-opioid receptors, yet it

is also a partial agonist at κ-opioid receptors (Bart et al., 2005; Mann et al., 2016). While these medications still require more research in relation to theoretical models, they provide evidence and support for the influence of endogenous opioids and dopamine in the treatment of alcohol use disorders.

Changes in GABA and glutamate. The GABA and glutamate systems have been implicated in the neuroadaptations created by alcohol use (Spanagel & Zieglglnsberger, 1997). However, this mechanism has been less clear cut. Glutamate is an excitatory neurotransmitter similarly implicated in incentive salience and reinforcement, while GABA operates as an inhibitory neurotransmitter (Banerjee, 2014). Alcohol is a N-methyl-D-aspartate (NMDA) antagonist, meaning it prevents glutamate from binding to NMDA receptors (Banerjee, 2014). While chronic alcohol use will bring about an increase in the number or density of NMDA receptors, the absence of alcohol (i.e., an NMDA antagonist) among those with chronic alcohol use or an alcohol use disorder may cause glutamate-induced NMDA activation and hyperactivity and can result in deleterious effects such as tremors, agitation, and seizures (Airagnes et al., 2019).

Animal studies have also shown that alcohol will bind to $GABA_A$ receptors in the ventral tegmental area inhibiting GABA firing (Davies, 2003). In turn, this allows dopamine neurons to fire, producing increasing the levels of dopamine released in the mesolimbic pathway (Chau et al., 2010; Steffensen et al., 2009). Also through animal models, researchers were able to study molecular changes that can occur during extended (forced) abstinence (Grimm et al., 2001; Spanagel, 2017; Venniro et al., 2016). These studies have particularly elucidated changes in the glutamate system, specifically increases in glutamate receptors in the nucleus accumbens that cause the nucleus accumbens to be more reactive or sensitive to

cues or reward (Conrad et al., 2008). Animal models have also shown a decrease in dopamine and serotonin release during withdrawal, which may contribute to increased negative affect that is also seen in humans in withdrawal (Clapp et al., 2008; Diana et al., 2003; Heinz et al., 1998; Koob & Volkow, 2016; Weiss et al., 1996).

From these findings, the medication, acamprosate, was developed to reduce the return to alcohol use in people who are treatment-seeking and has been approved by the FDA (Littleton, 1995). Acamprosate is believed to reduce hyperexcitability during withdrawal by acting as an ionotropic, glutamate receptor antagonist (NMDA) in the nucleus accumbens and presynaptically increasing affinity for binding on $GABA_A$ receptors (Banerjee, 2014; Leggio et al., 2008). Baclofen is another medication that has been approved in European countries and Australia for alcohol use disorder that is a $GABA_B$ receptor agonist (Agabio et al., 2018; Liu & Wang, 2017). It has been found to suppress common physical withdrawal symptoms from chronic alcohol use in rats (Colombo et al., 2006; Colombo & Gessa, 2018). Though other molecular changes occur during alcohol use, these systems involving dopamine, endogenous opioids, glutamate, and GABA have been most often utilized in pharmacological treatments and are supported by animal models.

Motivational Models

Several motivational models of addiction pull from animal and human literature research with one of the earliest being Solomon & Corbit's opponent-process theory of motivation (Solomon & Corbit, 1974). An opponent-process in the context of addiction is a biological response to a change in the system to return the system to homeostasis (Solomon & Corbit, 1974). In the opponent-process theory of motivation, the system utilizing the opponent-process is the emotional system. Using a substance greatly increases positive

affect, so the opponent-process would be to induce negative affect to rebalance the system. This opponent-process is reinforced automatically with frequent substance use, and over time, motivation for the substance is acquired through the normal functioning of the system.

Koob and Volkow's allostatic model of addiction built on this theory (Koob & Le Moal, 2001, 2008; Koob & Volkow, 2010, 2016). They proposed that three processes or stages are part of an "addiction cycle", including the binge/intoxication stage, withdrawal/negative affect stage, and preoccupation/anticipation stage (Koob & Volkow, 2010). These stages map on to neuroadaptations that occur in unique and shared systems in the brain. The binge/intoxication stage is primarily related to reward and incentive salience, which is associated with activity in the basal ganglia, ventral tegmental area, and ventral striatum during the initial "impulsive use" of alcohol and shifts to activity in the dorsal striatum during later during "compulsive use" and increased dopamine and opioid activity (Koob & Volkow, 2016). The withdrawal/negative affect stage pulls on the opponent-process theory and is primarily concerned with negative emotional states and stress. In the opponent-process theory, as explained above, substance use increases positive affect and activates the brain's reward system; however, an opponent process introduces negative affect to return the body to homeostasis and after repeated uses of a substance, the opponent process will lower the hedonic set point (Koob & Le Moal, 2008). These areas of activity are generally in the habenula and the extended amygdala. Finally, the preoccupation/anticipation phase consisting of heighted craving and impulsivity, and executive function deficits, that are associated with reduced activity in the prefrontal cortex, insula, and allocortex. These systems are proposed to mediate risk, maintenance, and relapse in substance use disorders.

Finally, Cox and Klinger's motivational model of alcohol use posits that people consciously decide whether or not to consume alcohol based on prior expectations of changes in affective states that will occur when using alcohol (Cox & Klinger, 1988). Distal or proximal factors are influential, but only to the extent in which they change the person's expectations. Unlike many of the previous models, this motivational model emphasizes the conscious decision-making that occurs rather than automatic or adaptive responses. The last portion of the model breaks down expectations of how alcohol will change the individual's current affective state, concluding that the expectation of an increase in positive affect (i.e., enhancement motives) or relief from negative affect (i.e., coping motives) are two reasons for people to drink.

Reward and Relief Model

In the three-pathway psychobiological model of craving for alcohol, Verheul, Van Den Brink, and Geerlings integrated the psychological, neurobiological, and pharmacological literature on craving and motivation with utility for the diagnosis and treatment of alcohol use disorder (Verheul et al., 1999). In this model, they posit three pathways based on craving type, which are reward, relief, and obsessive craving. Each pathway has a specific set of neurobiological and psychological components and associated symptoms and motives for drinking. Reward craving is typified by dopaminergic and opioidergic dysfunction, sensitivity to positive reinforcement, and social reward as a motive for drinking. Relief craving is defined by GABAergic dysfunction, sensitivity to negative reinforcement, and stress reductions and withdrawal relief as reasons for drinking. Finally, obsessive craving is determined by serotonergic dysfunction, impulsivity, and a lack of control. In more recent animal research, changes in the corticotropin releasing factor (CRF) system may have a

greater influence on stress and withdrawal relief (Koob, 2010; Simpson et al., 2020), and an updated three-pathway model would potentially include CRF and elevated norepinephrine in addition to GABA in association with relief craving.

Verheul and colleagues originally hypothesized obsessive craving as one of the three pathways in their model, but it is often not included in later analyses on the subject (Mann et al., 2009; Ooteman et al., 2006). Additionally, less support has been found for obsessive craving, and when it is examined, it is often combined with relief craving (Heinz et al., 2003). Indeed, more recent research, described below, focuses exclusively on reward and relief craving defined as the reward-relief phenotype.

Application in Precision Medicine

Ultimately, creating a phenotype should assist in treating people with alcohol use disorder through precision medicine (Litten et al., 2012, 2015). Precision medicine, also called personalized medicine, aims to match clients with an optimal treatment based on individual characteristics (Carrasco-Ramiro et al., 2017). Medical specialties, such as oncology and gastroenterology, have already begun to implement this approach in clinical settings (Jackson & Chester, 2015; Štimac & Franjić, 2016), but research has just begun in the mental health field with the development of the Research Domain Criteria by the National Institute on Mental Health (Cuthbert, 2014; Cuthbert & Insel, 2013; Insel et al., 2010) and the Alcohol Addiction Research Domain Criteria by the National Institute of Alcohol Abuse and Alcoholism (AARDoC) (Litten et al., 2015). The AARDoC aims to create a classification system for research by which to examine broad criteria of alcohol use disorder on different levels of analysis from social processes to changes in neurotransmission (Litten et al., 2015). While these domains have been primarily developed for research

purposes, by determining the exact mechanisms of action within these constructs, individual dysfunctions can be identified and resolved with specific treatments as well.

Based on the reward-relief phenotype as proposed by Verheul and colleagues (1999), some studies have already begun to test this phenotype with a precision medicine approach. Karl Mann and others (2009) developed the PREDICT study with an aim to determine if naltrexone and acamprosate would delay the return of a treatment-seeking sample to heavy drinking based on the reward-relief phenotype. It was proposed that those primarily drinking for the rewarding benefits of alcohol would have significant benefits when taking naltrexone based on the hypothesized opioidergic dysfunction among reward drinkers, and those drinking primarily for alcohol's relieving properties would have significant benefits when taking acamprosate based on the hypothesized glutamatergic dysfunction among relief drinkers (Mann et al., 2009; Verheul et al., 1999).

Using the PREDICT data and factor mixture modeling, Mann and colleagues (2018) identified four classes of reward/relief drinking: high reward/high relief, low reward/high relief, high reward/low relief, and low reward/low relief. They found a significant interaction between the high reward/low relief subgroup and treatment with naltrexone with an 83% decreased likelihood of heavy drinking throughout the 12-week treatment versus placebo. However, they did not find significant main effects or interactions between any other subgroups, naltrexone or acamprosate, and drinking outcomes during treatment. Additionally, they found that the high reward group displayed higher novelty seeking and lower depression and anxiety scores. The high relief group displayed lower novelty seeking and higher depression and anxiety scores.

Using a large, treatment-seeking sample, a study by Roos and others (Roos et al., 2017) similarly examined the effect of naltrexone and acamprosate by reward-relief phenotype. They found a slightly different set of subgroups using confirmatory factor analysis and factor mixture modeling with five classes defined as low reward/low relief, moderate reward/moderate relief, high reward/moderate relief, high relief/moderate reward, and high reward/high relief. They found a main effect of naltrexone assignment predicting percent of heavy drinking days at the week 16 assessment compared to placebo. Also, the high relief/moderate reward subgroup had significant interaction effects with acamprosate predicting percent of drinking days at the week 16 assessment and percent drinking days and percent heavy drinking days at the week 26 assessment. Notably, the interaction between the high reward/moderate relief subgroup and acamprosate was also significant in predicting percent of drinking days at the week 26 assessment. They did not find significant effects between any other subgroups, naltrexone, and drinking outcomes during treatment. Broadly, relief temptation was also found to be positively associated with depressive symptoms.

Another recent study examining the effect of naltrexone by reward-relief phenotype (Witkiewitz et al., 2019) found the same two-factor, four-class solution that Mann and previous studies have found (Glöckner-Rist et al., 2013; Mann et al., 2018). In addition, they found a significant interaction between the high reward/low relief subgroup and naltrexone in drinks per drinking day and percent of heavy drinking days during the 12-week treatment (Witkiewitz et al., 2019). Those treated with naltrexone in the high reward/low relief subgroup also reported less desire to drink over time, which supported the notion that naltrexone may reduce the rewarding effects of alcohol and preferentially improve treatment outcomes among reward drinkers.

Finally, a study specifically designed to examine reward-relief drinking categorized participants as reward, relief, or habit drinkers through a novel questionnaire (Burnette et al., 2021). They found that combined relief and habit drinkers scored lower on items reflecting reward drinking and higher on items reflecting relief drinking in a questionnaire examining reasons for drinking. Relief and habit drinkers also had greater alcohol use disorder severity and higher cue-elicited bilateral dorsal striatum activation compared to reward drinkers. They also found that relief and habit drinkers had higher depressive and trait anxiety scores than reward drinkers.

These studies conducted by Mann, Roos, Witkiewitz, and Burnette (Burnette et al., 2021; Mann et al., 2018; Roos et al., 2017; Witkiewitz et al., 2019) support portions of the reward-relief phenotype and its utility in precision medicine, but this phenotype needs to be explored further. The Mann and Witkiewitz studies examined drinking outcomes only through 12-week treatment but did not examine follow-up assessments. The Roos study examined drinking outcomes at one year but only to determine the efficacy of medications within subgroups. The reward-relief phenotype itself has been replicated and supported in numerous studies (Mann et al., 2018; Roos et al., 2017; Witkiewitz et al., 2019), but the stability of the phenotype across time has not been examined. Based on previous models like the allostatic model of addiction (Koob & Volkow, 2010, 2016) or incentive-sensitization theory (Robinson & Berridge, 1993), it is expected that an individual's reason or motivation for drinking would change across time. The rewarding benefits of alcohol may be reduced as the desire to relieve negative states increases. If a phenotype were stable across time, some treatments would always work best for a specific individual. However, if the phenotype changes over time, it may be necessary to determine where the individual currently lies

within the phenotype with a brief questionnaire or assessment for the correct treatment to be applied.

Aims and Hypotheses

In the current study, we first aimed to determine whether the reward-relief phenotype, as established from the Alcohol Abstinence Self-Efficacy questionnaire (Roos et al., 2017), can be replicated in a community, non-treatment-seeking sample and is stable from baseline to three months. For individuals within the phenotypic groups, we hypothesized that those with the least reward and relief drinking and those with greater relief drinking, regardless of reward drinking, would remain classified in those phenotypic groups. Those with the lowest reward and relief drinking were likely already drinking at low amounts, and we would not expect them to increase their motivation for the rewarding or relieving effects of alcohol. We expected that those primarily drinking to relieve negative states would continue to do so without treatment and were not likely to drink for more rewarding purposes if they were not already doing so. We also expected that those people drinking for primarily rewarding reasons would either shift to drinking to relieve negative states or to drinking less for either rewarding or relieving purpose. This was expected based on the information presented above, where individuals may start consuming alcohol to experience rewarding effects but tend to shift toward relieving effects later, potentially to receive the same feeling of reward as the hedonic set point continues to lower.

We also aimed to find if the reward-relief phenotype that has previously been found in two larger, treatment-seeking samples is stable from baseline to post-treatment (three to four months post-baseline) to extend the findings from Mann et al. and Roos et al. (Mann et al., 2018; Roos et al., 2017). For the individuals classified in the phenotype, we hypothesized

that those with the lowest reward and relief drinking and those higher in relief drinking, regardless of reward drinking, would not change groups from baseline to post-treatment. As stated before, though treatment is effective, it is thought that those drinking to relieve negative states will have the greatest consumption and consequences, and it may be the most difficult for them to recover. Treatment for alcohol use disorder can entail difficult withdrawal symptoms and heightened stress and negative affect. If an individual's previous coping mechanism for difficult states was using alcohol, reducing these negative states may continue to be a reason for using alcohol, even if they have reduced their alcohol use and consequences. We expected those drinking for rewarding reasons would shift toward lower reward and relief drinking, as they began to consume less and potentially reduce situations in which they would use alcohol for rewarding reasons.

Additionally, in our community sample, we aimed to explore if the reward-relief phenotype predicted alcohol consumption and consequences 18 months after the baseline assessment. We hypothesized that those with higher relief drinking, regardless of reward drinking, at baseline would have the highest consumption and consequences at 18 months. Previous models such as the incentive-sensitization model and the allostatic model of addiction posit that individuals using a substance like alcohol would shift from positive reinforcement to more compulsive use of alcohol that is negatively reinforced (Koob & Volkow, 2010, 2016; Robinson & Berridge, 1993). Based on these theories, we assumed that those who drink to relieve negative states, including any withdrawal symptoms, may result in heavier consumption and more consequences. We also hypothesized that overall consumption would decrease across time. Previous work in alcohol recovery has shown that people meeting criteria for alcohol dependence outside of treatment settings still exhibit self-

initiated change by reducing alcohol consumption (Dawson et al., 2005; Dearing et al., 2013).

For the two treatment samples, we hypothesized the reward-relief phenotype at baseline would predict alcohol consumption and consequences one year after treatment (fifteen to sixteen months post-baseline). For consumption and consequences, we hypothesized that those with higher relief drinking, regardless of reward drinking, at baseline would have the highest alcohol consumption and consequences at one year. We also hypothesized that alcohol consumption and consequences would decrease across time since all participants received treatment (i.e., medication, psychotherapy, or both) and were actively trying to reduce their alcohol consumption.

Method

Data Sources and Participants

This study consisted of secondary data analyses of three samples of individuals including: (1) participants recruited to study mechanisms of behavior change in a heavy drinking, non-treatment-seeking sample (i.e., the community sample), (2) participants with alcohol use disorder seeking treatment in Project Matching Alcoholism Treatment to Client Heterogeneity (MATCH; Project MATCH Research Group, 1993, 1997) and (3) participants with alcohol use disorder seeking treatment in the Combined Pharmacotherapies and Behavioral Interventions (COMBINE) Study (Anton et al., 2006; COMBINE Research Group, 2003).

Community sample. The community sample was recruited from the community in Albuquerque, New Mexico as part of the ABQ DrinQ study (Al-Khalil et al., 2021). Inclusion criteria comprised being 22 to 55 years old, reporting an Alcohol Use Disorders Identification Test (AUDIT) score of greater than 7 for females and greater than 8 for males having a breath alcohol level of 0.000 at screening, and being right-handed (due to neuroimaging components of the study). Exclusion criteria for this study included seeking treatment for alcohol use including mutual support groups like Alcoholics Anonymous, a history of brain injury or neurological diagnoses, meeting criteria for lifetime schizophrenia or bipolar disorder, a current substance use disorder diagnosis other than cannabis, any evidence of illicit drug use on urine drug screen other than cannabis, contraindications for magnetic resonance imaging (MRI) at any time throughout the study, a positive pregnancy test at any time throughout the study, an estimated IQ below 80, an inability to read or speak

English fluently, a history of severe alcohol withdrawal including seizures and tremors, and any belief by the study team that the participant was providing false information.

The study examined longitudinal mechanisms of change that underlie those who change or maintain their heavy drinking without psychosocial, behavioral, and neural intervention. Neural, behavioral, and self-report measures were collected at baseline, 3 months, 9 months, and 18 months. For this study, we utilized the self-report data from baseline, 3-month, and 18-month assessments to approximate the timepoints utilized in the treatment-seeking samples (e.g., baseline, 3- or 4-months post-baseline, and 15- or 16-months post-baseline).

Project MATCH. Project MATCH was a large scale, multisite, randomized clinical trial developed to determine if certain types of people with alcohol use disorder would respond differently to behavioral treatments for alcohol use including Twelve-Step Facilitation, Motivational Enhancement Therapy, and Cognitive-Behavioral Coping Skills Therapy (Project MATCH Research Group, 1993). Participants were recruited from outpatient or inpatient centers and from the community in Albuquerque, NM; Buffalo, NY; Farmington, CT; Milwaukee, WI; West Haven, CT; Charleston, SC; Houston, TX; Providence, RI; and Seattle, WA (Project MATCH Research Group, 1997). In total, there were 1,726 participants (n = 952 outpatient participants and n = 774 aftercare participants) who all received one of the three behavioral treatments (Project MATCH Research Group, 1997). Inclusion criteria for the study comprised of a current diagnosis of alcohol abuse or dependence based on the DSM-III-R (American Psychiatric Association, 1987), alcohol as the primary substance of concern, alcohol consumption 3 months before screening for the study, aged 18 years or older, a 6th grade reading level or higher, acceptance of treatment

randomization, ability to commute to treatment sessions, and prior detoxification when medically appropriate. Exclusion criteria included a current diagnosis of other substance dependence, intravenous drug use in the previous six months, current suicidal or homicidal ideation, probation or parole proceedings that would interfere with the study, residential instability, social instability, current severe psychosis, severe physical impairments leading to mental impairments, or participation in other treatment for alcohol-related problems not including mutual support groups like Alcoholics Anonymous. Greater detail on the methodology of Project MATCH has been previously reported (Project MATCH Research Group, 1993, 1997). In the current analyses, we used data from the baseline, post-treatment (i.e., three months post-baseline), and one-year post-treatment (i.e., 15 months post-baseline) assessments.

COMBINE. COMBINE was a large, multi-site, randomized clinical trial developed to determine if alcohol outcomes could be improved by combining behavioral and pharmacological treatments (COMBINE Research Group, 2003). These pharmacotherapies included naltrexone and acamprosate, and behavioral therapies included Medical Management and Combined Behavioral Intervention. Participants were seeking treatment for alcohol use disorder and were recruited from the community and by referral at 11 sites including in Providence, RI; Chapel Hill, NC; Boston, MA; Miami, FL; Charleston, SC; Albuquerque, NM; Philadelphia, PA; San Antonio, TX; Seattle, WA; Milwaukee, WI; and New Haven, CT. In total, there were 1,383 participants from all 11 sites. Inclusion criteria included was comprised of being 18 years of age or older; a current DSM-IV diagnosis of alcohol dependence (American Psychiatric Association, 1994); signing informed consent for the study; having alcohol consumption greater than 14 or 21 drinks (female or male

respectively) per week on average and 2 or more heavy drinking episodes (4 drinks for females or 5 drinks for males) in the 90 days prior to abstinence; minimum of 4 consecutive days of abstinence; a Clinical Institute Withdrawal Assessment for Alcohol score below 8; maximum of 21 days of abstinence prior to randomization; no more than 21 consecutive days of planned absence during the treatment period; identifying at least 1 "locator" person; and the ability to speak and understand English. Exclusion criteria included the current diagnosis of any psychological disorders requiring medication; current diagnosis of bulimia, anorexia, or dementia; current diagnosis of substance use dependence with the exception of nicotine, cannabis, or habitual caffeine use; taking any medications that would interact with study medications; significant medical disorders or sensitivity to study medications that cause safety concerns; elevated AST, ALT, or bilirubin; pregnant or nursing women or women not using adequate contraceptive methods; receiving treatment outside of the study; more than 7 days of inpatient treatment for substance use disorders in the previous 30 days; and participants who have prior use to study medications in the past 30 days. Greater detail on the methodology of COMBINE has been previously reported (Anton et al., 2006; COMBINE Research Group, 2003). In the current analyses, we used data from the baseline, post-treatment (i.e., 4 months post-baseline), and 1-year post-treatment (i.e., 16 months post-baseline) assessments.

Measures

Community sample.

Demographics. Demographic information, including gender, age, and race and ethnicity was collected at baseline and utilized in the current analyses.

Alcohol use. To measure alcohol consumption, the Form 90, a retrospective calendar-based assessment employing the Timeline Follow-Back method, was used to determine daily drinking patterns in the past 90 days (Sobell & Sobell, 1992). This method is the gold standard for retrospective self-report of alcohol use and has been shown to be reliable and accurate in many studies, even for heavy drinkers (Chow et al., 2017; Maisto et al., 2008; Miller & Del Boca, 1994; Pedersen et al., 2012; Sobell et al., 1996, 2003). At baseline and at the 18-month assessment, participants retrospectively reported daily drinking in the past 90 days. From those points, we calculated several alcohol use indicators including percent of drinking days (PDD), percent of heavy drinking days (PHD; defined as four or more drinks for women or five or more drinks for men), and the average number of drinks per drinking day (DDD). There were 2 missing responses at baseline (n = 187) and 41 missing responses at 18 months post-baseline (n = 148).

Reward-relief phenotype. To determine the phenotype of each participant, we utilized a portion of the Temptation scale of the Alcohol Abstinence Self-Efficacy questionnaire (DiClemente et al., 1994; Glöckner-Rist et al., 2013). The Alcohol Abstinence Self-Efficacy questionnaire is a 40-item questionnaire assessing feelings of confidence and temptation to drink alcohol in various situations including during social situations, physical discomfort, negative affect, and withdrawal symptoms. Each question has a range from zero to five with zero being not tempted or not confident at all and five being extremely tempted or extremely confident. We employed methods as laid out in previous articles (Glöckner-Rist et al., 2013) and used only 10 items total (5 for relief, 5 for reward) from the Temptation scale to determine each participant's reward-relief subtype with data from the baseline and 3-month assessments. In the community sample, there were zero missing data at baseline and 41

responses missing at three months post-baseline (n = 148). Cronbach's α for the relief and reward questions at baseline were α = 0.875 and 0.869, respectively, and at three months were α = 0.881 and 0.882.

Alcohol consequences. To measure alcohol consequences, we utilized the Short Inventory of Problems-Recent questionnaire (Blanchard et al., 2003). The Short Inventory of Problems-Recent is a 15-item questionnaire compiled from the original 50-item Drinker Inventory of Consequences-Recent to assess adverse consequences from drinking in the past 3 months in physical, intrapersonal, social responsibility, interpersonal, and impulse control domains (Miller et al., 1995). Each question has a Likert response scale from 0 to 3 based on frequency (0 = "Never" to 3 = "Daily or almost daily") with total scores ranging from 0 to 45. Higher scores indicate more consequences and/or higher frequency of consequences. For our current analyses, we utilized total scores from baseline and 18-month assessments. In the community sample, there were no missing responses at baseline and 41 responses missing at 18 months post-baseline (n = 148). Cronbach's α for the Short Inventory of Problems-Recent at baseline was α = 0.910 and at 18 months was α = 0.974.

Treatment-seeking samples.

Demographics. Demographic information, including gender, age, race and ethnicity, and treatment assignment, were collected at baseline and utilized in the current analyses. For Project MATCH, the treatment assignment variables included two, mutually exclusive binary variables for those receiving Cognitive-Behavioral Coping Skills Therapy or Motivational Enhancement Therapy. For COMBINE, the treatment assignment included three binary variables for those receiving acamprosate, naltrexone, and/or Combined Behavioral Intervention. In COMBINE, age was missing six responses (n = 1377).

Alcohol use. To measure alcohol use, the Form 90 was also used to assess daily drinking patterns in the past 90 days at baseline and at 1-year post-treatment (i.e., 15 months post-baseline for Project MATCH and 16 months post-baseline for COMBINE). We calculated PDD, PHD, and DDD from these timepoints. For Project MATCH, 744 responses were missing at baseline (n = 982) and 855 responses at follow-up (n = 871), and for COMBINE, 1 response was missing at baseline (n = 1382) and 497 responses were missing at follow-up (n = 885).

Reward-relief phenotype. To determine the phenotype of each participant, we utilized 10 items from the Temptation scale of the Alcohol Abstinence Self-Efficacy questionnaire (DiClemente et al., 1994; Glöckner-Rist et al., 2013) as described above at baseline and post-treatment (i.e., 3 months post-baseline for Project MATCH and 4 months post-baseline for COMBINE). In the Project MATCH sample, 42 responses were missing at baseline (n = 1684) and 184 at three months post-baseline (n = 1542). In COMBINE, 26 were missing at baseline (n = 1357), and 295 were missing at four months post-baseline (n = 1088). For Project MATCH, Cronbach's α for the relief and reward questions at baseline were α = 0.883 and 0.904, respectively, and at three months were α = 0.897 and 0.903. For COMBINE, Cronbach's α for the relief and reward questions at baseline were α = 0.875 and 0.916, respectively, and at four months were α = 0.912 and 0.944.

Alcohol consequences. To determine alcohol consequences, we utilized the Drinker Inventory of Consequences-Recent, a 45-item questionnaire that assesses adverse consequences from alcohol consumption in the past three months in physical, intrapersonal, social responsibility, interpersonal, and impulse control domains (Miller et al., 1995). Like the Short Inventory of Problems-Recent, each question has a Likert response scale from 0 to

3 based on frequency (0 = "Never" to 3 = "Daily or almost daily") with total scores ranging from 0 to 135. Higher scores indicate more consequences and/or higher frequency of consequences. For our current analyses, we utilized the total scores from baseline and 1-year post-treatment assessments (i.e., 15 months post-baseline for Project MATCH and 16 months post-baseline for COMBINE). At baseline for Project MATCH, 360 responses were missing (n = 1366), and at 15 months post-baseline, 818 responses were missing (n = 908). At baseline for COMBINE, 2 responses were missing (n = 1381), and at 16 months post-baseline, 418 responses were missing (n = 908). For Project MATCH, Cronbach's α for the Drinker Inventory of Consequences-Recent at baseline was $\alpha = 0.931$ and at 15 months was $\alpha = 0.960$. For COMBINE, Cronbach's α for the Drinker Inventory of Consequences-Recent at baseline was $\alpha = 0.926$ and at 16 months was $\alpha = 0.969$.

Analytic Approach

Descriptive statistics.

To better understand the data, we examined the means and standard deviations or number of responses and percentages of the covariates, follow-up data, and responses to the Alcohol Abstinence Self-Efficacy questionnaire. The covariates included age, gender, race/ethnicity (dichotomized as non-white vs. white and non-Hispanic), baseline drinking variables (PDD, PHD, and DDD), baseline recent drinking consequences, and treatment assignment for the two treatment samples. We also examined measures of central tendency and response rates of the follow-up data for the drinking variables and drinking consequences.

Latent profile analyses.

The first step to analyze the data was to use latent profile analysis at each time point to identify groups of individuals, called profiles, based on responses to specific indicators (Goodman, 1974; Lazarsfeld & Henry, 1968). This method is very similar to latent class analysis, although latent profile analysis typically includes continuous indicators. In latent profile analysis, categorical latent variables are identified based on the relationships between observed continuous or categorical indicators with an assumption of local independence between latent variables. Latent profile analysis estimates two types of parameters: item probability parameters and class probability parameters. Item probability parameters are the probabilities of responding to indicators given profile membership, and class probability parameters estimate the prevalence of individuals within each profile (Nylund et al., 2007). In each of our three samples, we determined the number of profiles based on responding patterns to the ten items on the Temptation subscale of the Alcohol Abstinence Self-Efficacy questionnaire at each time point, and the latent profiles represented the reward-relief phenotype for our study.

Model fit was determined using the Bayesian Information Criterion, adjusted Bayesian Information Criterion, and the Lo-Mendell-Rubin adjusted likelihood ratio test. The Bayesian Information Criterion is a fit index based on the log likelihood value of a model with penalties for a larger number of parameters and larger sample sizes. A lower Bayesian Information Criterion value indicates a model with better fit. The adjusted Bayesian Information Criterion is similar to the Bayesian Information Criterion except that it does not penalize additional parameters as harshly and does not have as much research. Parsimony and goodness of fit should be balanced by examining both criteria. The Lo-Mendell-Rubin adjusted likelihood ratio test provides a test of significant differences between a model with k

classes and k-1 classes, and if the test is statistically significant, the model with k classes would provide a better fit. At each time point for each sample, models were identified and compared for best fit. The number of classes were determined by a balance of theory and fit criteria. For the fit criteria, the best fitting model was indicated with the lowest Bayesian Information Criterion, lowest adjusted Bayesian Information Criterion, and significant Lo-Mendell-Rubin adjusted likelihood ratio test.

After determining the best fitting model based on theory and fit criteria, we confirmed adequate fit with posterior probabilities, entropy, and profile sizes. Posterior probabilities indicate the probability of most likely profile membership by the latent profile, and these values should approach one. Similarly, entropy is a measure of certainty, where values that approach one indicate greater certainty of correct classification. Finally, while there is not a cutoff for profile or class sizes in the literature, an often-used rule of thumb is classes comprised of less than 1% of the sample or with less than 25 individuals should be well-justified (Lubke & Neale, 2006). From there, we ran conditional latent profile analyses to determine the effect of covariates on the models. Covariates for the samples included age, gender, race/ethnicity, baseline drinking variables, baseline recent drinking consequences, and treatment assignment for the two treatment samples.

Latent transition analyses and covariates.

To determine the stability of classification within the reward-relief phenotype over time, we used a longitudinal, autoregressive model called latent transition analysis. Latent transition analysis allowed us to test the probability of transitioning between the phenotypic groups (i.e., latent profiles) identified at baseline and the follow-up time points (Collins & Wugalter, 1992). In other words, do individuals have the same expected classification in each

phenotype across time, or do they transition to a different phenotype across time? We determined the probability of transitioning between profiles with the transition probability matrix.

In order to interpret transitions in profiles over time it is important to first examine whether the latent profiles at each time point (baseline and follow-up) are measurement invariant (i.e., equivalent) across time with respect to the number of profiles and types of profiles (i.e., the means of the indicators). Thus, we first tested measurement invariance of the latent profiles across time by testing a fully invariant model in which the number of profiles and means of the indicators were constrained to be equal over time. We then compared the loglikelihood of the model that was constrained to the loglikelihood of a latent transition model in which the means of the indicators were allowed to vary. We compared the nested models using a corrected chi-square difference test to assess the invariance of the model longitudinally (Satorra & Bentler, 2010). If the models were invariant, we also ran latent transition models without covariates (i.e., unconditional model) and subsequently, with covariate predictors (i.e., conditional model) of latent profiles. In the models were not invariant then the transition probabilities are not interpretable (i.e., the latent profiles are not equivalent and thus transitions between them cannot be interpreted), and no additional models were tested.

Distal outcomes.

Finally, we determined differences in long-term outcomes based on the baseline latent profiles using distal outcome analysis through the manual Bolck–Croon–Hagenaars (BCH) three-step approach (Bakk et al., 2013; Bolck et al., 2004; Nylund-Gibson et al., 2019). Distal outcome analysis provided an assessment of mean differences in outcomes such as

alcohol consumption and consequences between profiles using Wald X^2 tests. Additionally, the manual BCH three-step approach allows for errors in the classification of individuals at baseline, and by manually advancing through the steps, greater flexibility is given in model specification (Nylund-Gibson et al., 2019).

Power Analyses

For the latent profile analyses, statistical power was estimated using an *a priori* Monte Carlo simulation study (Nylund et al., 2007). In each of the samples, we had power > 0.80 to detect four latent profiles using the Lo-Mendell-Rubin Adjusted likelihood ratio test and bootstrapped likelihood ratio test. For distal outcome analyses, we conducted power analyses in G*Power 3.1 (Faul et al., 2007, 2009). For all samples, we had power > 0.80 to detect medium effect sizes of distal outcome differences.

Results

Descriptive Statistics

Demographic information for the community sample and two treatment samples are presented in Table 1. Participants in all samples were primarily non-Hispanic, white (59.8% community sample to 80.0% treatment samples) and male (56.6% community sample to 75.7% treatment samples). Ages ranged from a mean age of 34.15 years old in the community sample to 44.55 years old in the COMBINE sample. As expected, the treatment-seeking samples reported greater frequency and quantity of alcohol use at baseline compared to the community sample. Additionally, from baseline to one-year post-treatment, the treatment samples had significantly lower PDD, PHD, DDD, and recent drinking consequences. The community sample had significantly lower PDD and recent drinking consequences.

The means and standard deviations for the 10 questions from the Alcohol Abstinence Self-Efficacy scale is shown in Table 2 for baseline and 3- or 4-months post-baseline (3 months post-baseline in the community sample and Project MATCH and 4 months post-baseline in the COMBINE study).

Latent Profile Analyses

Latent profile analyses were conducted for each of the three studies using the ten questions from the Alcohol Abstinence Self-Efficacy scale at baseline and at three months post-baseline for the community sample and Project MATCH and at four months post-baseline for COMBINE. The model fit statistics are presented in Table 3. For the community sample, the lowest values of the Bayesian Information Criterion and adjusted Bayesian Information Criterion indicated that the five-profile model would be the best fit, but the Lo-

Table 1. *Sample demographic characteristics and covariates for all studies at all timepoints.*

	Community Sample (N = 189)	Project MATCH (N = 1726)	COMBINE (N = 1383)
Baseline	N (%)	N (%)	N (%)
Gender			
Female	82 (43.4%)	419 (24.3%)	428 (30.9%)
Male	107 (56.6%)	1307 (75.7%)	955 (69.1%)
Race/Ethnicity			
White	113 (59.8%)	1381 (80.0%)	1062 (76.8%)
Black/African American	9 (4.8%)	169 (9.8%)	109 (7.9%)
Asian/Native Hawaiian/Pacific Islander	9 (4.8%)	2 (0.1%)	4 (0.3%)
American Indian or Alaska Native	39 (20.6%)	25 (1.4%)	18 (1.3%)
Latino/Hispanic	92 (48.7%)	141 (8.2%)	155 (11.2%)
Bi-Racial, Multi-Racial, or "Other"	--	8 (0.5%)	35 (2.5%)
Treatment Assignment			
Cognitive-Behavioral Coping Skills Therapy	--	567 (32.9%)	--
Motivational Enhancement Therapy	--	577 (33.4%)	--
Twelve-Step Facilitation	--	582 (33.7%)	--
Acamprosate	--	--	608 (44.0%)
Naltrexone	--	--	614 (44.4%)
Combined Behavioral Intervention	--	--	619 (44.8%)
	Mean (SD)	Mean (SD)	Mean (SD)
Age	34.15 (9.99)	40.23 (11.00)	44.55 (10.18)
Consequences from Drinking			
Short Inventory of Problems	10.03 (7.70)*	--	--
Drinker Inventory of Consequences	--	51.76 (23.31)*	47.61 (20.42)*
Drinking Variables			
Percent of Drinking Days	50.74 (26.57)*	65.77 (29.83)*	74.96 (25.06)*
Percent of Heavy Drinking Days	28.71 (26.90)	55.63 (31.29)*	65.54 (28.57)*
Drinks per Drinking Day	6.03 (3.79)	11.51 (7.41)*	12.47 (7.94)*
Long-term Follow-up			
Consequences from Drinking			
Short Inventory of Problems	7.42 (7.34)*	--	--
Drinker Inventory of Consequences	--	32.01 (25.50)*	19.89 (21.81)*

Drinking Variables			
Percent of Drinking Days	43.34 (30.74)*	27.58 (34.86)*	37.79 (37.69)*
Percent of Heavy Drinking Days	27.19 (29.95)	16.71 (28.30)*	26.15 (34.24)*
Drinks per Drinking Day	5.56 (3.37)	4.31 (5.27)*	4.67 (5.98)*

Note. * = significantly different from baseline to long-term follow-up at $p < 0.05$. For the community sample, participants were able to select multiple races and ethnicities for the community sample, so the total does not equal 100%. Additionally, treatments in COMBINE were combined so participants could be received both acamprosate and Combined Behavioral Intervention, for example. Follow-up for the community sample (n = 148) was completed at 18 months post-baseline, for Project MATCH (n = 871) at 15 months post-baseline, and for COMBINE (n = 886) at 16 months post-baseline.

Mendell-Rubin adjusted likelihood ratio indicated a two-profile model at baseline and either a two-profile or four-profile model at three months would fit the best.

In Project MATCH, the lowest values of the Bayesian Information Criterion and adjusted Bayesian Information Criterion indicated that the five-profile model would be the best fit. With the Lo-Mendell-Rubin adjusted likelihood ratio test, all models were significant except for the five-profile model at baseline. In COMBINE, the Bayesian Information Criterion and adjusted Bayesian Information Criterion also indicated the five-profile model as the best fit and the Lo-Mendell-Rubin adjusted likelihood ratio test showed all models were significant.

Given two through five profile models provided acceptable fit and considering prior research and concerns about overextraction of too many classes in latent variable mixture modeling (Bauer & Curran, 2003), we determined that a four-profile model would provide the best balance of parsimony and fit within all samples. This decision was further supported by the posterior probabilities, entropy, and class sizes for each of these models that indicated adequate fit. These four profiles include Low Relief-Low Reward, High Relief-Low Reward,

Table 2. *Means and standard deviations of Alcohol Abstinence Self-Efficacy questions for all studies at all timepoints.*

How tempted do you feel to drink in these situations?	Community Sample		Project MATCH		COMBINE	
	Baseline	Three Months	Baseline	Three Months	Baseline	Four Months
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
1. When I am feeling depressed.	2.86 (1.20)	2.59 (1.20)	3.24 (1.25)	2.58 (1.26)	3.24 (1.13)	2.33 (1.11)
2. When I am on vacation and want to relax.	3.93 (0.89)	3.81 (0.96)	3.31 (1.27)	2.61 (1.28)	2.54 (1.19)	2.73 (1.19)
3. When I am very worried.	2.57 (1.16)	2.41 (1.17)	3.16 (1.27)	2.45 (1.25)	3.08 (1.10)	2.18 (1.05)
4. When I am being offered a drink in a social situation.	3.97 (0.91)	3.83 (1.04)	3.20 (1.31)	2.45 (1.25)	3.48 (1.20)	2.57 (1.18)
5. When I am physically tired.	2.21 (1.08)	2.07 (1.05)	2.45 (1.23)	2.02 (1.16)	2.69 (1.14)	1.97 (1.00)
6. When I see others drinking at a bar or at a party.	3.74 (1.01)	3.49 (1.06)	3.23 (1.33)	2.54 (1.29)	3.47 (1.20)	2.57 (1.20)
7. When I sense everything is going wrong for me.	2.85 (1.29)	2.60 (1.33)	3.37 (1.31)	2.63 (1.34)	3.43 (1.18)	2.45 (1.17)
8. When people I used to drink with encourage me to drink.	3.55 (1.10)	3.41 (1.11)	2.91 (1.38)	2.27 (1.28)	3.35 (1.24)	2.47 (1.22)
9. When I am feeling angry inside.	2.69 (1.29)	2.51 (1.31)	3.29 (1.31)	2.62 (1.33)	3.31 (1.18)	2.31 (1.13)
10. When I am excited or celebrating with others.	4.16 (0.84)	4.06 (0.88)	3.45 (1.29)	2.71 (1.33)	3.61 (1.15)	2.68 (1.22)

Note. Alcohol Abstinence Self-Efficacy Scale has a range from zero to five for each question with zero being not tempted at all and five being extremely tempted.

Table 3. *Fit statistics for the latent profile analyses for all studies at all timepoints.*

Timepoint	BIC	aBIC	Entropy	LMR Adjusted LRT	BLRT	Smallest n (%)
Community Sample						
Baseline						
2 Profiles	5288.02	5189.83	0.859	458.36 (p = 0.036)	466.31 (p < 0.001)	85 (45%)
3 Profiles	5170.55	5037.51	0.858	172.15 (p = 0.083)	175.13 (p < 0.001)	39 (21%)
4 Profiles	5092.20	4924.32	0.872	133.69 (p = 0.198)	136.01 (p < 0.001)	33 (17%)
5 Profiles	5066.61	4863.88	0.888	81.84 (p = 0.463)	83.26 (p < 0.001)	17 (9%)
Three Months						
2 Profiles	4196.30	4098.19	0.906	427.96 (p = 0.007)	435.75 (p < 0.001)	64 (43%)
3 Profiles	4075.86	3942.95	0.885	172.27 (p = 0.095)	175.40 (p < 0.001)	43 (29%)
4 Profiles	4008.47	3840.75	0.913	120.17 (p = 0.040)	122.36 (p < 0.001)	21 (14%)
5 Profiles	3999.72	3797.19	0.921	62.58 (p = 0.222)	63.72 (p < 0.001)	7 (5%)
Project MATCH						
Baseline						
2 Profiles	50572.67	50474.19	0.914	6113.34 (p < 0.001)	6188.12 (p < 0.001)	591 (35%)
3 Profiles	48799.51	48666.08	0.875	1832.49 (p < 0.001)	1854.91 (p < 0.001)	327 (19%)
4 Profiles	47692.26	47523.88	0.866	1174.63 (p = 0.002)	1189.00 (p < 0.001)	307 (18%)
5 Profiles	47162.53	46959.21	0.858	604.09 (p = 0.106)	611.48 (p < 0.001)	263 (16%)
Three Months						
2 Profiles	45348.23	45249.74	0.907	6078.93 (p < 0.001)	6154.19 (p < 0.001)	743 (48%)
3 Profiles	43827.72	43694.30	0.883	1581.69 (p < 0.001)	1601.27 (p < 0.001)	368 (24%)
4 Profiles	42755.91	42587.54	0.879	1138.50 (p < 0.001)	1152.60 (p < 0.001)	322 (21%)
5 Profiles	42280.70	42077.39	0.867	549.18 (p = 0.002)	555.98 (p < 0.001)	272 (18%)
COMBINE						
Baseline						
2 Profiles	39169.76	39071.28	0.886	4161.19 (p < 0.001)	4213.53 (p < 0.001)	514 (37%)
3 Profiles	37625.68	37492.26	0.877	1603.41 (p < 0.001)	1623.58 (p < 0.001)	243 (18%)
4 Profiles	36785.79	36617.43	0.858	907.97 (p = 0.007)	919.39 (p < 0.001)	204 (15%)

5 Profiles	36273.68	36070.38	0.855	584.26 (p = 0.028)	591.61 (p < 0.001)	123 (9%)
Four Months						
2 Profiles	28944.08	28845.61	0.922	5093.20 (p < 0.001)	5159.36 (p < 0.001)	515 (47%)
3 Profiles	27359.25	27225.84	0.907	1640.50 (p = 0.001)	1661.81 (p < 0.001)	258 (24%)
4 Profiles	26704.85	26536.51	0.900	722.01 (p = 0.018)	731.38 (p < 0.001)	179 (16%)
5 Profiles	26043.28	25840.01	0.904	729.08 (p = 0.002)	738.55 (p < 0.001)	130 (12%)

Note. BIC = Bayesian Information Criterion. aBIC = sample size adjusted Bayesian Information Criterion. LMR Adjusted LRT = Lo-Mendell-Rubin Adjusted Likelihood Ratio Test. BLRT= Bootstrapped Likelihood Ratio Test.

Low Relief-High Reward, and High Relief-High Reward groups. The final profile counts and proportions are shown in Table 4. Next, we ran conditional latent profile analyses (i.e., with covariates) to determine if profile membership was significantly altered by the inclusion of covariates. The final profile counts and proportions for the conditional latent profile analyses are also presented in Table 4 and did not appear to remarkably alter profile membership for any of the samples.

Latent Transition Analyses and Covariates

Latent transition analyses were conducted for each of the three studies with the four-profile solutions at each time point. First, we tested measurement invariance, then we examined transition probabilities (unconditional models) and effects of covariates (conditional models) for those latent transition models that were invariant.

For the community sample, we found the latent transition model was invariant across time (X^2 (40) = 23.019, p = 0.986). Within the model, the Low Relief-Low Reward group appeared to be the most stable over time with the probability of being in that same profile from baseline to three months post-baseline at 0.926 and 0.712 for the unconditional and conditional models. The High Relief-Low Reward and Low Relief-High Reward groups were most likely to stay in their profiles for both models, and if they did switch groups, they were most likely to move to the Low Relief-Low Reward group over time. Additionally, the High Relief-High Reward group was most likely to stay in their profile, or if they did switch groups, to move to the Low Relief-High Reward or High Relief-Low Reward groups over time. These results were consistent when covariates were included. The final counts and proportions of the unconditional and conditional latent transition analyses are shown in Table 4. The means and standard errors of the indicators of the latent transition analyses (i.e., the Alcohol Abstinence Self-Efficacy

Table 4. *Final profile counts and proportions based on the most likely latent profile membership for all models in the current study.*

Sample and Model	Baseline N (%)				Three to Four Months Post-Baseline N (%)			
Community Sample	Low Relief - Low Reward	High Relief - Low Reward	Low Relief - High Reward	High Relief - High Reward	Low Relief - Low Reward	High Relief - Low Reward	Low Relief - High Reward	High Relief - High Reward
Unconditional LPA	33 (17%)	41 (22%)	70 (37%)	45 (24%)	48 (32%)	21 (14%)	43 (29%)	36 (24%)
Conditional LPA	33 (18%)	43 (23%)	65 (35%)	46 (24%)	46 (31%)	20 (14%)	49 (33%)	32 (22%)
Unconditional LTA	35 (19%)	36 (19%)	74 (39%)	44 (23%)	54 (29%)	31 (16%)	61 (32%)	43 (23%)
Conditional LTA	34 (18%)	39 (21%)	68 (36%)	46 (25%)	59 (32%)	30 (16%)	56 (30%)	42 (22%)
Outcome Analysis	33 (17%)	41 (22%)	70 (37%)	45 (24%)	--	--	--	--
Project MATCH								
Unconditional LPA	307 (18%)	365 (22%)	394 (23%)	622 (37%)	512 (33%)	355 (23%)	322 (21%)	357 (23%)
Conditional LPA	71 (9%)	136 (18%)	221 (29%)	334 (44%)	200 (29%)	160 (22%)	179 (25%)	172 (24%)
Unconditional LTA	275 (16%)	381 (22%)	305 (18%)	756 (44%)	622 (36%)	391 (23%)	347 (20%)	357 (21%)
Conditional LTA	58 (8%)	138 (18%)	181 (23%)	392 (51%)	250 (33%)	145 (19%)	210 (27%)	164 (21%)
Outcome Analysis	307 (18%)	365 (22%)	394 (23%)	622 (37%)	--	--	--	--
COMBINE								
Unconditional LPA	204 (15%)	317 (23%)	424 (31%)	431 (31%)	385 (35%)	339 (31%)	179 (16%)	192 (18%)
Conditional LPA	207 (15%)	283 (21%)	451 (33%)	427 (31%)	380 (35%)	332 (30%)	185 (17%)	192 (18%)
Unconditional LTA	121 (9%)	377 (27%)	283 (20%)	600 (43%)	632 (46%)	379 (27%)	244 (18%)	126 (9%)
Conditional LTA	126 (9%)	374 (27%)	290 (21%)	582 (43%)	581 (42%)	393 (29%)	246 (18%)	152 (11%)
Outcome Analysis	204 (15%)	317 (23%)	424 (31%)	431 (31%)	--	--	--	--

Note. LPA = Latent profile analysis. LTA = Latent transition analysis. Unconditional = without covariates. Conditional = with covariates. For the community sample and Project MATCH, the second timepoint was at three months post-baseline. For COMBINE, the second timepoint was at four months post-baseline.

Table 5. *Latent transition probabilities from the unconditional model for all samples in the current study.*

Baseline Profile	Three to Four Month Post-Baseline Profile			
Community Sample	Low Relief – Low Reward (N = 54; 29%)	High Relief – Low Reward (N = 31; 16%)	Low Relief – High Reward (N = 61; 32%)	High Relief – High Reward (N = 43; 23%)
Low Relief – Low Reward (N = 35; 19%)	0.926	0.037	0.000	0.037
High Relief – Low Reward (N = 36; 19%)	0.211	0.547	0.150	0.092
Low Relief – High Reward (N =74; 39%)	0.228	0.020	0.649	0.103
High Relief – High Reward (N = 44; 23%)	0.043	0.167	0.126	0.663
Project MATCH	Low Relief – Low Reward (N = 622; 36%)	High Relief – Low Reward (N = 391; 23%)	Low Relief – High Reward (N = 347; 20%)	High Relief – High Reward (N = 357; 21%)
Low Relief – Low Reward (N = 275; 16%)	0.767	0.111	0.074	0.048
High Relief – Low Reward (N = 381; 22%)	0.375	0.483	0.044	0.099
Low Relief – High Reward (N = 305; 18%)	0.366	0.073	0.510	0.050
High Relief – High Reward (N = 756; 44%)	0.246	0.213	0.219	0.322
COMBINE	Low Relief – Low Reward (N = 632; 46%)	High Relief – Low Reward (N = 379; 27%)	Low Relief – High Reward (N = 244; 18%)	High Relief – High Reward (N = 126; 9%)
Low Relief – Low Reward (N = 121; 9%)	0.625	0.248	0.063	0.064

High Relief – Low Reward (N = 377; 27%)	0.456	0.480	0.016	0.049
Low Relief – High Reward (N = 283; 20%)	0.433	0.079	0.453	0.035
High Relief – High Reward (N = 600, 43%)	0.294	0.269	0.221	0.216

Note. Entropy was 0.872, 0.866, and 0.875 for the community sample, Project MATCH, and COMBINE, respectively. Final profile counts and proportions are based on the most likely latent profile membership. The community sample and Project MATCH were both analyzed at three months post-baseline and COMBINE was at four months post-baseline.

Table 6. *Latent transition probabilities from the conditional model for all samples in the current study.*

Baseline Profile	Three to Four Month Post-Baseline Profile			
Community Sample	Low Relief – Low Reward (N = 59; 32%)	High Relief – Low Reward (N = 30; 16%)	Low Relief – High Reward (N = 56; 30%)	High Relief – High Reward (N = 42; 22%)
Low Relief – Low Reward (N = 34; 18%)	0.712	0.087	0.000	0.201
High Relief – Low Reward (N = 39; 21%)	0.335	0.483	0.108	0.074
Low Relief – High Reward (N = 68; 36%)	0.197	0.000	0.623	0.179
High Relief – High Reward (N = 46; 25%)	0.127	0.157	0.217	0.499
Project MATCH	Low Relief – Low Reward (N = 250; 33%)	High Relief – Low Reward (N = 145; 19%)	Low Relief – High Reward (N = 210; 27%)	High Relief – High Reward (N = 164; 21%)
Low Relief – Low Reward (N = 58; 8%)	0.723	0.075	0.134	0.067
High Relief – Low Reward (N = 138; 18%)	0.440	0.370	0.083	0.106
Low Relief – High Reward (N = 181; 23%)	0.400	0.064	0.502	0.034
High Relief – High Reward (N = 392; 51%)	0.207	0.208	0.262	0.323
COMBINE	Low Relief – Low Reward (N = 581; 42%)	High Relief – Low Reward (N = 393; 29%)	Low Relief – High Reward (N = 246; 18%)	High Relief – High Reward (N = 152;11%)
Low Relief – Low Reward (N = 126; 9%)	0.599	0.262	0.068	0.071

High Relief – Low Reward (N = 374; 27%)	0.446	0.480	0.017	0.057
Low Relief – High Reward (N = 290; 21%)	0.434	0.097	0.430	0.039
High Relief – High Reward (N = 582, 43%)	0.313	0.264	0.221	0.202

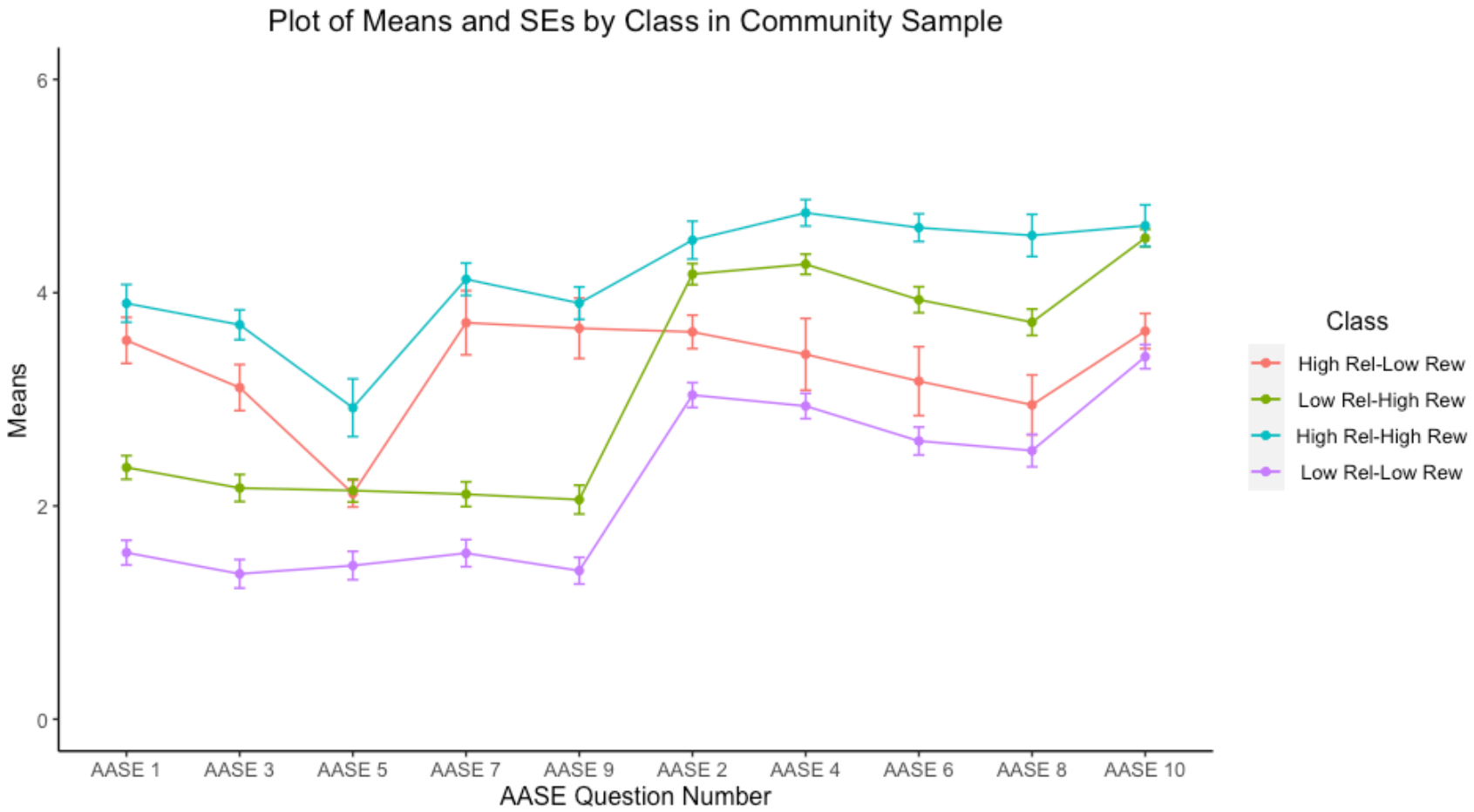
Note. Entropy was 0.905, 0.879, and 0.875 for the community sample, Project MATCH, and COMBINE, respectively. Final profile counts and proportions are based on the most likely latent profile membership. The community sample and Project MATCH were both analyzed at three months post-baseline and COMBINE was at four months post-baseline.

questions) are shown in Figure 1. The latent transition probabilities for the unconditional models and conditional models are shown in Tables 5 and 6, respectively. We also looked at the odds ratios for the covariates predicting profile membership as shown in Table 7 with the Low Relief-Low Reward group as the reference group. There were no significant covariates effects in the community sample (i.e., the 95% confidence interval for the odds ratios include 1.0).

For Project MATCH and COMBINE, we did not find invariance over time for the latent transition analyses (X^2 (40) = 266.003, p < 0.001; X^2 (40) = 640.912, p < 0.001). However, when examining the differences in the means and standard errors between the non-invariant (i.e., unconstrained) and invariant (i.e., constrained) models for both samples, as shown in Table 8, there were few discrepancies. On average, the means for each profile was slightly higher for the non-invariant models at baseline compared to the invariant models and slightly lower at three or four months later for the non-invariant models compared to the invariant models. The proportion of individuals in each profile was also slightly variable from the non-invariant to the invariant models as is displayed in Table 8. For Project MATCH, this included more individuals likely classified in the Low Relief-Low Reward and Low Relief-High Reward groups in the non-invariant model at baseline compared to the invariant model. Additionally, individuals were more likely to be classified in the High Relief-High Reward group in the non-invariant model at three months compared to the invariant model.

For COMBINE, we found similar results. More individuals were likely classified in the Low Relief-Low Reward and Low Relief-High Reward groups in the non-invariant model at baseline compared to the invariant model. Additionally, individuals were more likely to be classified in the High Relief-Low Reward and High Relief-High Reward groups in the non-invariant model at three months compared to the invariant model. While traditionally non-

Figure 1. *Mean indicator responses and standard errors for the unconditional latent transition analyses in the community sample.*



Note: SEs = Standard errors. AASE = Alcohol Abstinence Self-Efficacy questionnaire. Rel = Relief and Rew = Reward. In the community sample (N = 189), Low Relief – Low Reward = 33 (17%), High Relief – Low Reward = 41 (22%), Low Relief – High Reward = 70 (37%), and High Relief – High Reward = 45 (24%).

Table 7. *Odds ratios for demographic covariates for all samples by profile.*

	High Relief-Low Reward vs. Low Relief-Low Reward	Low Relief-High Reward vs. Low Relief-Low Reward	High Relief-High Reward vs. Low Relief-Low Reward
Community Sample	OR [CI]	OR [CI]	OR [CI]
Baseline			
Gender	1.739 [0.369, 8.186]	1.241 [0.390, 3.945]	2.470 [0.537, 11.365]
Age	0.994 [0.917, 1.077]	0.962 [0.897, 1.032]	0.933 [0.856, 1.017]
Non-Hispanic White	2.128 [0.531, 8.530]	1.516 [0.495, 4.638]	2.558 [0.446, 14.676]
3 Months			
Gender	3.799 [0.508, 28.407]	1.391 [0.325, 5.948]	1.204 [0.189, 7.692]
Age	0.997 [0.920, 1.081]	1.055 [0.979, 1.138]	0.966 [0.887, 1.052]
Non-Hispanic White	0.687 [0.130, 3.638]	2.008 [0.459, 8.792]	3.431 [0.734, 16.050]
Project MATCH			
Baseline			
Gender	0.493 [0.206, 1.182]	1.082 [0.457, 2.560]	0.556 [0.266, 1.161]
Non-Hispanic White	3.019 [0.980, 9.301]	1.332 [0.556, 3.192]	1.616 [0.735, 3.553]
Age	0.990 [0.959, 1.022]	0.956 [0.922, 0.992]*	0.951 [0.924, 0.979]*
CBT	1.630 [0.691, 3.846]	1.463 [0.635, 3.371]	1.533 [0.731, 3.216]
MET	1.312 [0.596, 2.888]	0.958 [0.420, 2.186]	0.912 [0.461, 1.804]
3 Months			
Gender	0.792 [0.432, 1.451]	1.038 [0.595, 1.813]	0.922 [0.497, 1.711]
Non-Hispanic White	2.658 [0.998, 7.080]	1.563 [0.799, 3.059]	1.331 [0.645, 2.750]
Age	1.009 [0.984, 1.036]	0.976 [0.951, 1.002]	0.978 [0.953, 1.003]
CBT	0.956 [0.454, 2.014]	1.742 [0.986, 3.075]	0.831 [0.448, 1.541]
MET	1.766 [0.935, 3.336]	1.858 [0.940, 3.673]	1.220 [0.657, 2.266]
COMBINE			
Baseline			
Gender	1.238 [0.711, 2.156]	0.654 [0.356, 1.201]	1.848 [1.101, 3.102]
Non-Hispanic White	2.009 [1.184, 3.408]*	1.853 [1.085, 3.165]*	1.709 [1.062, 2.751]*

Age	0.999 [0.976, 1.022]	0.965 [0.941, 0.989]*	0.967 [0.946, 0.989]*
Acamprosate	1.238 [0.776, 1.974]	0.969 [0.579, 1.620]	1.099 [0.705, 1.712]
Naltrexone	1.027 [0.654, 1.612]	0.715 [0.428, 1.196]	0.958 [0.626, 1.466]
CBI	0.924 [0.582, 1.466]	1.128 [0.698, 1.822]	0.879 [0.571, 1.352]
4 Months			
Gender	1.343 [0.831, 2.168]	1.204 [0.690, 2.100]	1.225 [0.731, 2.053]
Non-Hispanic White	1.016 [0.676, 1.529]	2.075 [1.136, 3.789]*	1.193 [0.687, 2.072]
Age	0.990 [0.972, 1.008]	0.969 [0.947, 0.991]*	0.962 [0.937, 0.987]
Acamprosate	0.906 [0.644, 1.276]	1.234 [0.807, 1.888]	0.654 [0.409, 1.048]
Naltrexone	0.929 [0.658, 1.310]	0.995 [0.597, 1.659]	0.765 [0.484, 1.208]
CBI	0.967 [0.684, 1.368]	0.901 [0.607, 1.338]	0.633 [0.397, 1.009]

Note. CBT = Cognitive Behavioral Coping Skills Therapy. MET = Motivational Enhancement Therapy. CBI = Combined Behavioral Intervention. * = does not include 1 in the confidence interval. OR = odds ratio. CI = 95% confidence interval.

Table 8. *Means, standard errors, and proportions of AASE questions by class in invariant and noninvariant models for Project MATCH and COMBINE samples.*

	Invariant				Noninvariant			
	Low Relief -Low Reward	Low Relief -High Reward	High Relief -Low Reward	High Relief -High Reward	Low Relief -Low Reward	Low Relief -High Reward	High Relief -Low Reward	High Relief -High Reward
Project MATCH								
Baseline								
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	266 (15.51%)	319 (18.60%)	378 (22.04%)	753 (43.84%)	313 (18.26%)	397 (23.14%)	383 (22.29%)	624 (36.32%)
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
AASE 1	1.62 (0.05)	2.32 (0.12)	3.52 (0.08)	3.97 (0.06)	1.72 (0.07)	2.64 (0.12)	3.68 (0.09)	4.11 (0.07)
AASE 3	1.52 (0.04)	2.22 (0.13)	3.37 (0.08)	3.88 (0.06)	1.63 (0.07)	2.58 (0.11)	3.54 (0.09)	4.06 (0.08)
AASE 5	1.31 (0.03)	1.99 (0.09)	2.41 (0.07)	3.07 (0.05)	1.35 (0.04)	2.19 (0.09)	2.48 (0.08)	3.16 (0.06)
AASE 7	1.58 (0.04)	2.28 (0.15)	3.62 (0.09)	4.25 (0.06)	1.63 (0.06)	2.67 (0.15)	3.79 (0.09)	4.42 (0.07)
AASE 9	1.57 (0.04)	2.30 (0.15)	3.53 (0.08)	4.16 (0.05)	1.64 (0.06)	2.64 (0.13)	3.68 (0.10)	4.30 (0.07)
AASE 2	1.69 (0.05)	3.33 (0.10)	2.80 (0.08)	3.96 (0.04)	1.88 (0.09)	3.57 (0.11)	2.94 (0.09)	4.09 (0.05)
AASE 4	1.42 (0.04)	3.26 (0.11)	2.35 (0.10)	4.10 (0.05)	1.55 (0.08)	3.53 (0.14)	2.50 (0.12)	4.23 (0.05)
AASE 6	1.45 (0.05)	3.33 (0.10)	2.37 (0.09)	4.21 (0.05)	1.56 (0.08)	3.57 (0.14)	2.45 (0.12)	4.33 (0.05)
AASE 8	1.29 (0.03)	2.78 (0.13)	2.12 (0.09)	3.93 (0.05)	1.39 (0.06)	3.05 (0.17)	2.20 (0.12)	4.01 (0.06)
AASE 10	1.55 (0.06)	3.64 (0.10)	2.71 (0.10)	4.32 (0.04)	1.73 (0.10)	3.86 (0.12)	2.80 (0.13)	4.43 (0.04)
Three Months								
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	648 (37.73%)	364 (21.21%)	396 (23.07%)	309 (17.98%)	574 (33.45%)	351 (20.46%)	399 (23.26%)	392 (22.83%)
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
AASE 1	1.62 (0.05)	2.32 (0.12)	3.52 (0.08)	3.97 (0.06)	1.52 (0.05)	2.13 (0.09)	3.29 (0.11)	3.84 (0.07)
AASE 3	1.52 (0.04)	2.22 (0.13)	3.37 (0.08)	3.88 (0.06)	1.44 (0.05)	1.97 (0.09)	3.15 (0.12)	3.67 (0.07)

AASE 5	1.31 (0.03)	1.99 (0.09)	2.41 (0.07)	3.07 (0.05)	1.27 (0.03)	1.87 (0.07)	2.28 (0.10)	3.01 (0.08)
AASE 7	1.58 (0.04)	2.28 (0.15)	3.62 (0.09)	4.25 (0.06)	1.49 (0.05)	2.04 (0.10)	3.40 (0.12)	4.08 (0.07)
AASE 9	1.57 (0.04)	2.30 (0.15)	3.53 (0.08)	4.16 (0.05)	1.49 (0.06)	2.08 (0.11)	3.35 (0.11)	4.02 (0.07)
AASE 2	1.69 (0.05)	3.33 (0.10)	2.80 (0.08)	3.96 (0.04)	1.58 (0.05)	3.14 (0.12)	2.58 (0.10)	3.68 (0.07)
AASE 4	1.42 (0.04)	3.26 (0.11)	2.35 (0.10)	4.10 (0.05)	1.35 (0.04)	3.07 (0.11)	2.16 (0.10)	3.83 (0.08)
AASE 6	1.45 (0.05)	3.33 (0.10)	2.37 (0.09)	4.21 (0.05)	1.38 (0.04)	3.15 (0.12)	2.22 (0.12)	4.02 (0.08)
AASE 8	1.29 (0.03)	2.78 (0.13)	2.12 (0.09)	3.93 (0.05)	1.24 (0.03)	2.60 0.13)	1.95 (0.10)	3.82 (0.09)
AASE 10	1.55 (0.06)	3.64 (0.10)	2.71 (0.10)	4.32 (0.04)	1.45 (0.04)	3.48 (0.12)	2.55 (0.12)	4.06 (0.07)
COMBINE								
Baseline								
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	121 (8.77%)	289 (20.89%)	379 (27.47%)	592 (42.87%)	211 (15.29%)	390 (28.24%)	350 (25.36%)	430 (31.11%)
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
AASE 1	1.49 (0.05)	2.37 (0.15)	3.07 (0.12)	3.95 (0.09)	2.01 (0.11)	2.69 (0.08)	3.47 (0.10)	4.16 (0.06)
AASE 3	1.41 (0.04)	2.22 (0.15)	2.84 (0.12)	3.80 (0.09)	1.84 (0.11)	2.54 (0.08)	3.27 (0.09)	4.01 (0.06)
AASE 5	1.34 (0.03)	2.21 (0.16)	2.40 (0.08)	3.19 (0.06)	1.72 (0.10)	2.45 (0.07)	2.75 (0.08)	3.33 (0.07)
AASE 7	1.52 (0.04)	2.43 (0.15)	3.29 (0.13)	4.23 (0.09)	2.02 (0.10)	2.83 (0.11)	3.72 (0.09)	4.44 (0.06)
AASE 9	1.44 (0.04)	2.28 (0.12)	3.14 (0.12)	4.06 (0.11)	1.97 (0.12)	2.65 (0.10)	3.57 (0.09)	4.34 (0.06)
AASE 2	1.76 (0.06)	3.66 (0.22)	2.95 (0.05)	4.16 (0.04)	2.12 (0.11)	3.83 (0.10)	3.18 (0.09)	4.29 (0.05)
AASE 4	1.55 (0.07)	3.66 (0.22)	2.63 (0.07)	4.26 (0.04)	1.83 (0.09)	3.91 (0.10)	2.83 (0.15)	4.42 (0.06)
AASE 6	1.55 (0.06)	3.67 (0.22)	2.57 (0.07)	4.31 (0.04)	1.84 (0.08)	3.88 (0.10)	2.77 (0.16)	4.48 (0.05)
AASE 8	1.41 (0.06)	3.53 (0.24)	2.51 (0.06)	4.17 (0.05)	1.64 (0.08)	3.71 (0.10)	2.70 (0.16)	4.36 (0.06)
AASE 10	1.65 (0.07)	3.82 (0.21)	2.79 (0.07)	4.33 (0.04)	1.98 (0.09)	4.03 (0.10)	3.02 (0.13)	4.50 (0.05)
Four Months								
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	548 (39.67%)	275 (19.92%)	394 (28.52%)	164 (11.89%)	470 (34.02%)	229 (16.60%)	436 (31.58%)	246 (17.79%)
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)

AASE 1	1.49 (0.05)	2.37 (0.15)	3.07 (0.12)	3.95 (0.09)	1.37 (0.05)	2.03 (0.11)	2.82 (0.10)	3.66 (0.08)
AASE 3	1.41 (0.04)	2.22 (0.15)	2.84 (0.12)	3.80 (0.09)	1.32 (0.04)	1.88 (0.09)	2.55 (0.09)	3.50 (0.09)
AASE 5	1.34 (0.03)	2.21 (0.16)	2.40 (0.08)	3.19 (0.06)	1.25 (0.04)	1.94 (0.08)	2.20 (0.06)	3.01 (0.10)
AASE 7	1.52 (0.04)	2.43 (0.15)	3.29 (0.13)	4.23 (0.09)	1.41 (0.05)	2.10 (0.10)	2.96 (0.11)	3.92 (0.08)
AASE 9	1.44 (0.04)	2.28 (0.12)	3.14 (0.12)	4.06 (0.11)	1.35 (0.04)	1.91 (0.10)	2.83 (0.11)	3.67 (0.09)
AASE 2	1.76 (0.06)	3.66 (0.22)	2.95 (0.05)	4.16 (0.04)	1.68 (0.05)	3.47 (0.13)	2.78 (0.08)	3.99 (0.08)
AASE 4	1.55 (0.07)	3.66 (0.22)	2.63 (0.07)	4.26 (0.04)	1.42 (0.05)	3.43 (0.11)	2.54 (0.07)	4.06 (0.08)
AASE 6	1.55 (0.06)	3.67 (0.22)	2.57 (0.07)	4.31 (0.04)	1.42 (0.05)	3.48 (0.13)	2.49 (0.07)	4.08 (0.08)
AASE 8	1.41 (0.06)	3.53 (0.24)	2.51 (0.06)	4.17 (0.05)	1.29 (0.04)	3.37 (0.14)	2.43 (0.08)	3.94 (0.09)
AASE 10	1.65 (0.07)	3.82 (0.21)	2.79 (0.07)	4.33 (0.04)	1.53 (0.05)	3.57 (0.12)	2.70 (0.08)	4.01 (0.08)

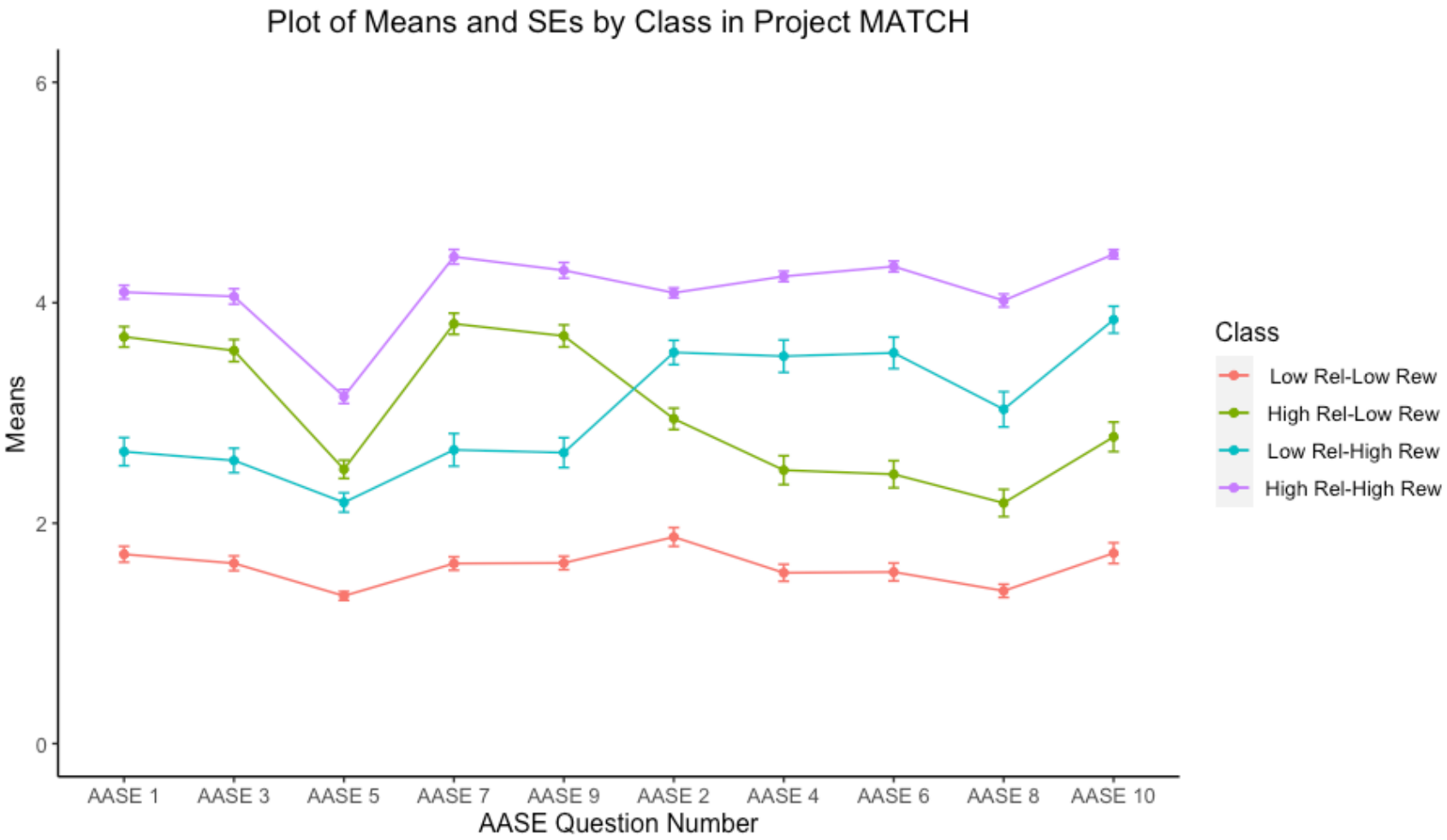
Note. AASE = Alcohol Abstinence Self-Efficacy questionnaire. SE = standard error.

invariant latent transition models would not be examined any further, given the similarities of results in the non-invariant and invariant models, we still present the latent transition analyses for the Project MATCH and COMBINE samples, which should be interpreted with caution.

In the Project MATCH sample, we found the Low Relief-Low Reward group also appeared to be the most stable over time with the probability of staying in that profile from baseline to three months post-baseline at 0.767 and 0.723 for the unconditional and conditional models (see Figure 2). Similarly, the High Relief-Low Reward and Low Relief-High Reward groups are most likely to stay in their profiles or move to the Low Relief-Low Reward groups. However, for the High Relief-High Reward group, they are most likely to stay in their group, but if they move, they are most likely to move to the Low Relief-Low Reward group for the unconditional model. In the conditional model, we found that each profile was most likely to stay in that profile from baseline to three months, except for the High Relief-Low Reward group, which was most likely to shift to the Low Relief-Low Reward group. The latent transition probabilities for the unconditional models and conditional models are shown in Tables 5 and 6, respectively. We also looked at the odds ratios for the covariates predicting profile membership as shown in Table 7 with the Low Relief-Low Reward group as the reference group. We found at baseline individuals who were younger were more likely to be classified in the Low Relief-High Reward and High Relief-High Reward group, than those in the Low Relief-Low Reward group.

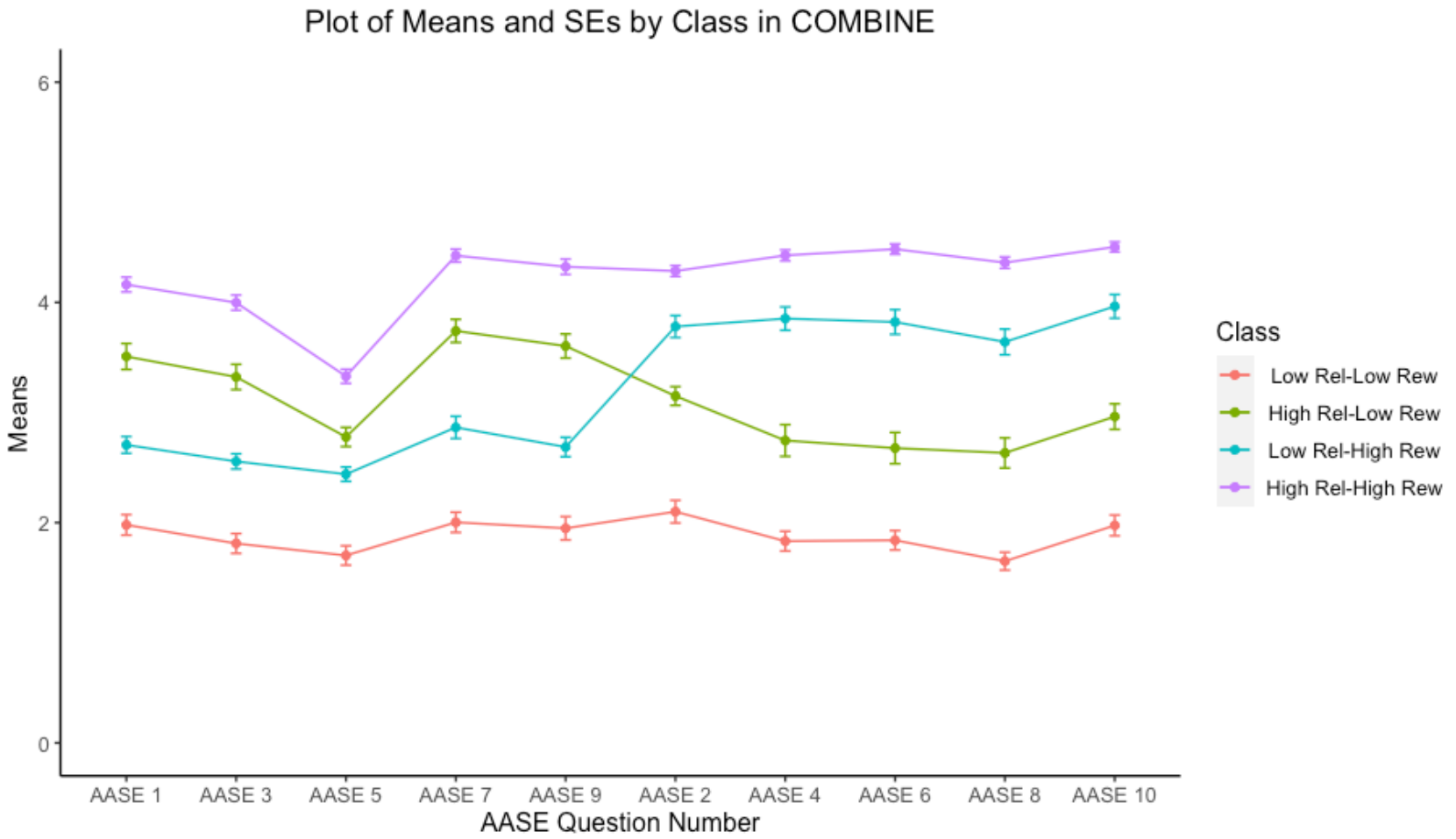
In the COMBINE sample, the Low Relief-Low Reward group continued to be the most stable over time with the probability of staying in that profile from baseline to four months post-baseline at 0.625 and 0.599 for the unconditional and conditional models (see Figure 3). Similarly, the High Relief-Low Reward and Low Relief-High Reward groups are most likely to stay in their profiles or move to the Low Relief-Low Reward groups. However, for the High

Figure 2. *Mean indicator responses and standard errors for the unconditional latent transition analyses in Project MATCH.*



Note: SEs = Standard errors. AASE = Alcohol Abstinence Self-Efficacy questionnaire. Rel = Relief and Rew = Reward. In Project MATCH (N = 1688), Low Relief – Low Reward = 307 (18%), High Relief – Low Reward = 365 (22%), Low Relief – High Reward = 394 (23%), and High Relief – High Reward = 622 (37%).

Figure 3. *Mean indicator responses and standard errors for the unconditional latent transition analyses in COMBINE.*



Note: SEs = Standard errors. AASE = Alcohol Abstinence Self-Efficacy questionnaire. Rel = Relief and Rew = Reward. In COMBINE (N = 1376), Low Relief – Low Reward = 204 (15%), High Relief – Low Reward = 317 (23%), Low Relief – High Reward = 424 (31%), and High Relief – High Reward = 431 (31%).

Relief-High Reward group, they are most likely to move to the Low Relief-Low Reward group for both the unconditional and conditional models. For both models, those in the baseline High Relief-High Reward group were not likely to stay in the High Relief-High Reward group at four months post-baseline. In the conditional model, only those in the Low Relief-Low Reward and High Relief-Low Reward groups were most likely to stay in the same group. Those in the Low Reward-High Reward and High Relief-High Reward groups were most likely to be classified into the Low Relief-Low Reward group four months later. The latent transition probabilities for the unconditional models and conditional models are shown in Tables 5 and 6, respectively. We also looked at the odds ratios for the covariates predicting profile membership as shown in Table 7 with the Low Relief-Low Reward group as the reference group. Those who were non-Hispanic white were more likely to be classified in the High Relief-Low Reward, Low Relief-High Reward, High Relief-High Reward groups compared to the Low Relief-Low Reward group. At baseline, we also found individuals who were younger were more likely classified in the Low Relief-High Reward and High Relief-High Reward group than those in the Low Relief-Low Reward group. At four months post-baseline, we found those who were non-Hispanic white and younger were more likely to be classified in the Low Relief-High Reward group than the Low Relief-Low Reward group.

Distal Outcomes

Finally, we examined the differences in distal outcomes between profiles based on the baseline latent profile model using the manual BCH three-step approach. The results of these analyses are shown in Table 9. In the community sample, there were significant differences between profiles in drinking consequences, frequency of alcohol use (PDD), frequency of heavy alcohol use (PHD), and intensity of alcohol use (DDD). Those in the High Relief-High Reward

group had the highest consequences and alcohol consumption scores and the High Relief-Low Reward group had the second highest consequences and frequency of alcohol consumption (PDD). Surprisingly, those in the Low Relief-Low Reward group had the second highest PHDD and DDD. We also found that alcohol consequences and PDD reduced over time in the community sample, as shown in Table 1.

In the Project MATCH sample, significant differences were found between profiles in drinking consequences, frequency of heavy alcohol use (PHD), and intensity of alcohol use (DDD), but not the frequency of alcohol use (PDD). The High Relief-Low Reward and High Relief-High Reward groups in Project MATCH had the most consequences and greatest alcohol consumption. We also found that consequences and alcohol consumption variables were significantly reduced over time in the Project MATCH sample, as shown in Table 1.

In the COMBINE sample, significant differences were found between profiles in drinking consequences and frequency of alcohol use (PDD), but not in frequency of heavy alcohol use (PHD) or intensity of drinking (DDD). In COMBINE, the High Relief-High Reward group had the highest consequences, PHDD, and DDD, and the Low Relief-High Reward group had the highest PDD. We also found that consequences and alcohol consumption variables were significantly reduced over time in COMBINE sample, as shown in Table 1.

Table 9. *Distal outcomes for all samples by profile.*

	Short Inventory of Problems	Percent of Drinking Days	Percent of Heavy Drinking Days	Drinks per Drinking Day
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
Community Sample				
Low Relief – Low Reward (17%)	2.46 (0.75)[abc]	34.60 (5.80)[c]	24.70 (6.10)[c]	6.43 (0.70)
High Relief – Low Reward (22%)	8.14 (1.06)[ade]	42.50 (5.50)	21.10 (5.00)[e]	4.72 (0.61)[e]
Low Relief – High Reward (37%)	4.99 (0.93)[bdf]	39.30 (4.50)[f]	21.49 (4.10)[f]	4.83 (0.45)[f]
High Relief – High Reward (24%)	13.10 (1.48)[cef]	55.20 (5.70)[cf]	42.30 (5.70)[cef]	6.80 (0.63)[ef]
	Drinker Inventory of Consequences	Percent of Drinking Days	Percent of Heavy Drinking Days	Drinks per Drinking Day
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
Project MATCH				
Low Relief – Low Reward (18%)	19.23 (3.80)[a]	23.45 (4.67)	12.81 (3.57)[a]	3.34 (0.66)[c]
High Relief – Low Reward (22%)	39.32 (3.19)[ade]	31.70 (3.87)	24.19 (3.46)[ad]	4.04 (0.47)
Low Relief – High Reward (23%)	19.98 (1.60)[df]	24.50 (2.40)	11.01 (1.67)[df]	3.76 (0.34)[f]
High Relief – High Reward (37%)	26.90 (1.88)[ef]	30.35 (2.27)	19.66 (1.91)[f]	4.92 (0.37)[cf]
COMBINE				
Low Relief – Low Reward (15%)	15.19 (1.84)[ac]	33.40 (3.00)[b]	24.67 (2.77)	6.15 (0.58)
High Relief – Low Reward (23%)	20.98 (1.74)[a]	37.53 (2.71)	25.25 (2.39)	6.12 (0.48)
Low Relief – High Reward (31%)	17.34 (1.19)[f]	41.55 (2.21)[b]	26.74 (2.03)	5.97 (0.32)
High Relief – High Reward (31%)	23.94 (1.48)[cf]	36.69 (2.05)	27.13 (1.89)	6.51 (0.37)

Note: Superscripts indicate significant differences ($p < 0.05$) between profiles based on Wald X^2 test. [a] = Low-Low versus High-Low. [b] = Low-Low versus Low-High. [c] = Low-Low versus High-High. [d] = High-Low versus Low-High. [e] = High-Low versus High-High. [f] = Low-High versus High-High. Distal outcomes were measured at 18 months post-baseline for the community sample, 15 months post-baseline for Project MATCH, and 16 months for COMBINE and do not account for change from baseline.

Discussion

In this study, we found support for most of the hypotheses put forward. First, we found that the reward-relief phenotype characterized by four latent profiles replicated in a community sample, as it had been found in the treatment samples in this study and prior research (Mann et al., 2018; Roos et al., 2017). This included four groups varying by relief and reward drinking: Low Relief-Low Reward, High Relief-Low Reward, Low Relief-High Reward, and High Relief-High Reward. We found this phenotype could be identified and was stable across time in the community sample. Interestingly, invariance was not found for the latent transition models for the Project MATCH and COMBINE samples, suggesting that treatment might alter the phenotype with lower mean levels of temptation across all phenotype groups following treatment. Yet, the overall structure of the phenotype was consistent, even if the means and class proportions varied across time in the treatment-seeking samples. We also found that there were some transitions in phenotypic group assignments from baseline to three- or four-months post-baseline in the community and treatment samples. While individuals primarily stayed in the same phenotypic group from baseline to three- or four-months post-baseline, those in the High Relief-High Reward group in the treatment-seeking sample were most likely to transition to the Low Relief-Low Reward group following treatment.

Drinking consequences decreased significantly over time across all three samples. Alcohol consumption also significantly decreased over time in both treatment samples, and frequency of drinking (PDD) decreased significantly over time for the community sample, which is consistent with prior literature (Anton et al., 2006; Project MATCH Research Group, 1997; Tucker et al., 2020). Baseline profiles were also significantly related to differences in long-term consequences and alcohol consumption with those in the High Relief-High Reward and High

Relief-Low Reward groups having the greatest consequences and alcohol consumption across the long-term follow-ups over a year after baseline in all samples.

Clinical Implications

These findings are important for multiple reasons. First, in finding that the phenotype replicates in treatment-seeking and non-treatment-seeking samples, it could be applied to recommend certain treatments. For example, recent work has shown that Low Relief-High Reward drinkers may benefit most from naltrexone (Mann et al., 2018; Roos et al., 2017; Witkiewitz et al., 2019). Identifying this phenotype could also be used to identify those at higher risk for consequences due to alcohol use. In the non-treatment seeking community sample, we found that those in the High Relief-High Reward group at baseline had the highest alcohol consumption and consequences 18 months later. Personalized feedback interventions that are tailored to an individual's phenotype and that provide information about risk for greater alcohol use and consequences could be used to help resolve ambivalence about changing alcohol use (Miller & Rollnick, 2012).

Second, we found the four-profile phenotype model fit well and was stable over time for the community sample, but not for the treatment-seeking samples. Even though the baseline models for all samples had predictive validity, the non-invariant model across time fit better for Project MATCH and COMBINE. While this was an unexpected result, we did see that these distinctions were relatively minor overall and may speak to the change that occurs in alcohol treatment compared to the drinking reductions in the community. As shown in Table 2, while the Project MATCH and COMBINE samples did not necessarily have higher scores for the Alcohol Abstinence Self-Efficacy questions than the community sample at baseline, they did report greater reductions in Alcohol Abstinence Self-Efficacy scores over time. Additionally, with the

exception of three questions, the Project MATCH and COMBINE samples had lower scores on the Alcohol Abstinence Self-Efficacy questions at three or four months compared to the community sample at three months. Thus, individuals who completed a treatment for alcohol use disorder found relieving or rewarding situations less tempting over time, whereas individuals who did not undergo treatment did not report a change in temptation to drink over time. While statistically this makes the latent transition analysis more difficult to interpret, clinically this is what we would hope to see in clinical trials. Even with these changes, the broad structure of the phenotype appears to be consistent over time, even if the means of the indicators and class proportions are not equivalent over time.

Third, our results showed that this phenotype has predictive validity regarding alcohol consumption and consequences. Our results did not entirely support the theory that those with more chronic drinking would drink for relieving reasons and have higher consequences and consumption (Koob & Volkow, 2016). However, those with higher relieving or rewarding drinking tended to have higher consumption and consequences.

Implications for Neurobiological Theories of Addiction

It was somewhat surprising to find that in almost every group in every sample, people in those groups were most likely to stay in those groups over three or four months, regardless of their resulting consumption or consequences. We had assumed that given their likely reduction in drinking, it would be less tempting to drink in rewarding or relieving situations overall. However, it is possible that given the neuroadaptations that have already occurred (Breese et al., 2011; Koob & Volkow, 2010), even a year after treatment, individuals could have continued to find it tempting to drink during rewarding or relieving situations and chose not to. While neurobiological changes occur constantly, significant alterations that occur in addiction, such as

increases in glutamate receptors in the nucleus accumbens or reduced tonic dopamine firing in the prefrontal cortex, have been reinforced over years (Koob & Volkow, 2016). New learning patterns can be developed over time that may reduce that desire to use alcohol whether through medications or behavioral changes (Helstrom et al., 2016); however, the neural changes that occurred throughout addiction may continue to persist, such as hypersensitivity in dopamine systems to substances and decreased sensitivity to natural rewards (Robinson & Berridge, 1993; Stewart & Vezina, 1988). Yet, with the lack of reinforcement through alcohol use, the strength of those pathways and conditioned responses should continue to fade over time (Leung & Corbit, 2017), causing continued reduced desire to drink in rewarding or relieving situations.

Strengths and Limitations

There were several strengths in this paper. We analyzed community and treatment-seeking samples and participants from a variety of cities across the United States, providing for a broader generalization of findings. We also utilized large samples of treatment-seeking participants, which gave us enough power to find small to medium effect sizes. This is the first study to include a non-treatment-seeking sample when investigating this phenotype and to examine the stability of the phenotype over time for non-treatment-seeking and treatment-seeking samples. Additionally, we were able to examine how these reasons for drinking at baseline could influence consequences and alcohol consumption a year after treatment to examine longer-term functioning and predictive utility of the phenotype.

There were also several limitations that should be taken into account. First, our sample was comprised primarily of non-Hispanic, white men. Future research should focus on examining this phenotype for stability and consistency in a more diverse sample, especially racially and ethnically diverse samples, to justify its use in clinical settings. Second, there is no

definite solution with model fit indices, so model selection was based off prior research and the best judgement of the authors. Additionally, these models are probabilistic, and misclassification is always a possibility. Third, it is possible that the results have been impacted by attrition and missing data in each of these datasets, and we cannot fully describe how this may have changed the study results.

Future Directions

In the future, we would recommend developing a questionnaire specifically examining this reward-relief phenotype. While the Alcohol Abstinence Self-Efficacy questionnaire and others have been used before to determine the reward-relief phenotype of various samples (Glöckner-Rist et al., 2013; Mann et al., 2018; Roos et al., 2017), a questionnaire explicitly designed to examine the phenotype would be preferable from a statistical and clinical standpoint. Additionally, it will be vital to have explicit cutoff scores to replicate this phenotype easily in clinical settings. One questionnaire that has already been developed with the reward-relief phenotype in mind is the UCLA Reward, Relief, Habit Drinking Scale (RRHDS) (Burnette et al., 2021). While this appears to be a short, easy to score questionnaire, it does limit participants by categorizing them as reward, relief, or habit drinkers without allowing for a mix of reward and relief drinking. It will be important to continue to investigate the RRHDS questionnaire and potentially other questionnaires that allow for a mixture of reward and relief drinking.

Ultimately, this phenotype will need more research in relation to precision medicine. Some efforts have already examined if certain pharmacological treatments apply more effectively to individuals in certain groups (Mann et al., 2018; Roos et al., 2017; Witkiewitz et al., 2019). So far, studies have found significant interactions with Low Relief-High Reward groups and naltrexone predicting drinking outcomes (Mann et al., 2018; Witkiewitz et al., 2019).

Additionally, in Roos et al. (2017) which found slightly different reward and relief groups, the high relief/moderate reward and high reward/moderate relief groups had significant interaction effects with acamprosate predicting drinking outcomes. In the future, a study that randomizes individuals by phenotype into pharmacological treatments will greatly assist in understanding how this phenotype can best be used in precision medicine. More research will especially be needed with other treatments, since there have not been any studies that have investigated how the phenotype aligns with psychological or behavioral therapies without pharmacological intervention. Behavioral treatments for alcohol use disorder often focus on changing behavior (i.e., reducing alcohol use and consequences) in a variety of methods. Individuals who drink for rewarding reasons may benefit more from treatments like Community Reinforcement Approach or Cognitive-Behavioral Treatment, which both have specific focuses on social networks and social activities that do not include drinking (Epstein & McCrady, 2009; Hunt & Azrin, 1973). For individuals who drink for relieving reasons, they may improve more from a treatment like Mindfulness-Based Relapse Prevention, which focuses on non-judgmental awareness of body sensations, emotions, and thoughts that may be uncomfortable (Bowen et al., 2009).

Overall, we found the four-profile reward-relief phenotype replicated in treatment-seeking individuals with alcohol use disorder recruited for alcohol use disorder clinical trials and non-treatment seeking heavy drinkers recruited from the community. The four-profile reward-relief phenotype was stable over time for the community sample and predictive of drinking outcomes for all samples. This phenotype, which is founded on basic behavioral science, appears to have support for its clinical utility. Though further research is warranted to continue to develop measures that could be used in clinical practice, there is evidence that this phenotype

could be implemented when it comes to identifying specific treatments that may be most effective for people with alcohol use disorder.

References

Agabio, R., Sinclair, J. M., Addolorato, G., Aubin, H. J., Beraha, E. M., Caputo, F., Chick, J. D., de La Selle, P., Franchitto, N., Garbutt, J. C., Haber, P. S., Heydtmann, M., Jaury, P., Lingford-Hughes, A. R., Morley, K. C., Müller, C. A., Owens, L., Pastor, A., Paterson, L. M., … Leggio, L. (2018). Baclofen for the treatment of alcohol use disorder: the Cagliari Statement. *The Lancet Psychiatry*, *5*(12), 957–960. https://doi.org/10.1016/S2215-0366(18)30303-1

Airagnes, G., Ducoutumany, G., Laffy-Beaufils, B., Le Faou, A. L., & Limosin, F. (2019). Alcohol withdrawal syndrome management: Is there anything new? *La Revue de Médecine Interne*, *40*(6), 373–379. https://doi.org/10.1016/J.REVMED.2019.02.001

Akbar, M., Egli, M., Cho, Y. E., Song, B. J., & Noronha, A. (2018). Medications for alcohol use disorders: An overview. *Pharmacology and Therapeutics*, *185*, 64–85. https://doi.org/10.1016/j.pharmthera.2017.11.007

Al-Khalil, K., Vakamudi, K., Witkiewitz, K., & Claus, E. D. (2021). Neural correlates of alcohol use disorder severity among nontreatment-seeking heavy drinkers: An examination of the incentive salience and negative emotionality domains of the alcohol and addiction research domain criteria. *Alcoholism: Clinical and Experimental Research*, *45*(6), 1200–1214. https://doi.org/10.1111/acer.14614

American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders (3rd ed., rev.; DSM-III-R)* (3rd ed., r). American Psychiatric Association.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders (4th ed.; DSM-IV)* (4th ed.). American Psychiatric Association.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental*

Disorders (5th ed.). American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596

Anton, R. F., O'Malley, S. S., Ciraulo, D. A., Cisler, R. A., Couper, D., Donovan, D. M., Gastfriend, D. R., Hosking, J. D., Johnson, B. A., LoCastro, J. S., Longabaugh, R., Mason, B. J., Mattson, M. E., Miller, W. R., Pettinati, H. M., Randall, C. L., Swift, R., Weiss, R. D., Williams, L. D., & Zweben, A. (2006). Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *JAMA*, *295*(17), 2003–2017. https://doi.org/10.1001/jama.295.17.2003

Babor, T. F., Hofmann, M., DelBoca, F. K., Hesselbrock, V., Meyer, R. E., Dolinsky, Z. S., & Rounsaville, B. (1992). Types of alcoholics, I: Evidence for an empirically derived typology based on indicators of vulnerability and severity. *Archives of General Psychiatry*, *49*(8), 599–608. https://doi.org/10.1001/archpsyc.1992.01820080007002

Bakk, Z., Tekle, F. B., & Vermunt, J. K. (2013). Estimating the association between latent class membership and external variables using bias-adjusted three-step approaches. *Sociological Methodology*, *43*(1), 272–311. https://doi.org/10.1177/0081175012470644

Banerjee, N. (2014). Neurotransmitters in alcoholism: A review of neurobiological and genetic studies. *Indian Journal of Human Genetics*, *20*(1), 20–31. https://doi.org/10.4103/0971-6866.132750

Bart, G., Schluger, J. H., Borg, L., Ho, A., Bidlack, J. M., & Kreek, M. J. (2005). Nalmefene induced elevation in serum prolactin in normal human volunteers: Partial kappa opioid agonist activity? *Neuropsychopharmacology*, *30*(12), 2254–2262. https://doi.org/10.1038/sj.npp.1300811

Bauer, D. J., & Curran, P. J. (2003). Distributional Assumptions of Growth Mixture Models:

Implications for Overextraction of Latent Trajectory Classes. *Psychological Methods*, *8*(3), 338–363. https://doi.org/10.1037/1082-989X.8.3.338

Blanchard, K. A., Morgenstern, J., Morgan, T. J., Labouvie, E. W., & Bux, D. A. (2003). Assessing consequences of substance use: Psychometric properties of the inventory of drug use consequences. *Psychology of Addictive Behaviors*, *17*(4), 328–331. https://doi.org/10.1037/0893-164X.17.4.328

Bogenschutz, M. P., Scott Tonigan, J., & Pettinati, H. M. (2009). Effects of alcoholism typology on response to naltrexone in the COMBINE study. *Alcoholism: Clinical and Experimental Research*, *33*(1), 10–18. https://doi.org/10.1111/j.1530-0277.2008.00804.x

Bolck, A., Croon, M., Hagenaars, J., Bolck, A., Croon, M., & Hagenaars, J. (2004). Estimating latent structure models with categorical variables: One-step versus three-step estimators. *Political Analysis*, *12*(1), 3–27.

Bowen, S., Chawla, N., Collins, S. E., Witkiewitz, K., Hsu, S., Grow, J., Clifasefi, S., Garner, M., Douglass, A., Larimer, M. E., & Marlatt, A. (2009). Mindfulness-based relapse prevention for substance use disorders: A pilot efficacy trial. *Substance Abuse*, *30*(4), 295–305. https://doi.org/10.1080/08897070903250084

Breese, G. R., Sinha, R., & Heilig, M. (2011). Chronic alcohol neuroadaptation and stress contribute to susceptibility for alcohol craving and relapse. *Pharmacology and Therapeutics*, *129*(2), 149–171. https://doi.org/10.1016/j.pharmthera.2010.09.007

Burnette, E. M., Grodin, E. N., Schacht, J. P., & Ray, L. A. (2021). Clinical and Neural Correlates of Reward and Relief Drinking. *Alcoholism: Clinical and Experimental Research*, *45*(1), 194–203. https://doi.org/10.1111/acer.14495

Carrasco-Ramiro, F., Peiró-Pastor, R., & Aguado, B. (2017). Human genomics projects and

precision medicine. *Gene Therapy*, *24*(9), 551–561. https://doi.org/10.1038/gt.2017.77

Centers for Disease Control and Prevention. (2013). *Report — Alcohol-Attributable Deaths, U.S., By Sex, Excessive Use*. Alcohol Related Disease Impact (ARDI) Application. https://nccd.cdc.gov/DPH_ARDI/Default/Report.aspx?T=AAM&P=f6d7eda7-036e-4553-9968-9b17ffad620e&R=d7a9b303-48e9-4440-bf47-070a4827e1fd&M=8E1C5233-5640-4EE8-9247-1ECA7DA325B9&F=&D

Centers for Disease Control and Prevention. (2018). *Data on Excessive Drinking | CDC*. https://www.cdc.gov/alcohol/data-stats.htm

Chau, P., Höifödt-Lidö, H., Löf, E., Söderpalm, B., & Ericson, M. (2010). Glycine receptors in the nucleus accumbens involved in the ethanol intake-reducing effect of acamprosate. *Alcoholism: Clinical and Experimental Research*, *34*(1), 39–45. https://doi.org/10.1111/j.1530-0277.2009.01063.x

Chow, P. I., Lord, H. R., MacDonnell, K., Ritterband, L. M., & Ingersoll, K. S. (2017). Convergence of online daily diaries and timeline followback among women at risk for alcohol exposed pregnancy. *Journal of Substance Abuse Treatment*, *82*, 7–11. https://doi.org/10.1016/j.jsat.2017.08.004

Clapp, P., Bhave, S. V, & Hoffman, P. L. (2008). How adaptation of the brain to alcohol leads to dependence: a pharmacological perspective. *Alcohol Research & Health : The Journal of the National Institute on Alcohol Abuse and Alcoholism*, *31*(4), 310–339. http://www.ncbi.nlm.nih.gov/pubmed/20729980

Cloninger, C. R. (1987). Neurogenetic adaptive mechanisms in alcoholism. *Science*, *236*, 410–416. https://doi.org/10.1126/science.2882604

Cloninger, C. R. (1995). The psychobiological regulation of social cooperation. *Nature*

Medicine, *1*(7), 623–625. https://doi.org/10.1038/nm0795-623

Cloninger, C. R., Bohman, M., & Sigvardsson, S. (1981). Inheritance of alcohol abuse: Cross-fostering analysis of adopted men. *Archives of General Psychiatry*, *38*(8), 861–868. https://doi.org/10.1001/archpsyc.1981.01780330019001

Collins, L. M., & Wugalter, S. E. (1992). Latent class models for stage-sequential dynamic latent variables. *Multivariate Behavioral Research*, *27*(1), 131–157. https://doi.org/10.1207/s15327906mbr2701_8

Colombo, G., & Gessa, G. L. (2018). Suppressing Effect of Baclofen on Multiple Alcohol-Related Behaviors in Laboratory Animals. *Frontiers in Psychiatry*, *9*. https://doi.org/10.3389/FPSYT.2018.00475

Colombo, G., Serra, S., Vacca, G., Carai, M. A. M., & Gessa, G. L. (2006). Baclofen-induced suppression of alcohol deprivation effect in Sardinian alcohol-preferring (sP) rats exposed to different alcohol concentrations. *European Journal of Pharmacology*, *550*(1–3), 123–126. https://doi.org/10.1016/j.ejphar.2006.08.052

COMBINE Research Group. (2003). Testing combined pharmacotherapies and behavioral interventions in alcohol dependence: Rationale and methods. *Alcoholism: Clinical and Experimental Research*, *27*(7), 1107–1122. https://doi.org/10.1111/j.1530-0277.2003.tb02873.x

Conrad, K. L., Tseng, K. Y., Uejima, J. L., Reimers, J. M., Heng, L. J., Shaham, Y., Marinelli, M., & Wolf, M. E. (2008). Formation of accumbens GluR2-lacking AMPA receptors mediates incubation of cocaine craving. *Nature*, *454*(7200), 118–121. https://doi.org/10.1038/nature06995

Cox, W. M., & Klinger, E. (1988). A Motivational Model of Alcohol Use. *Journal of Abnormal*

Psychology, *97*(2), 168–180. https://doi.org/10.1037/0021-843X.97.2.168

Cuthbert, B. N. (2014). The RDoC framework: Facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. *World Psychiatry*, *13*(1), 28–35. https://doi.org/10.1002/wps.20087

Cuthbert, B. N., & Insel, T. R. (2013). Toward the future of psychiatric diagnosis: The seven pillars of RDoC. *BMC Medicine*, *11*(1). https://doi.org/10.1186/1741-7015-11-126

Davies, M. (2003). The role of GABAA receptors in mediating the effects of alcohol in the central nervous system. *Journal of Psychiatry and Neuroscience*, *28*(4), 263–274. /pmc/articles/PMC165791/

Dawson, D. A., Grant, B. F., Stinson, F. S., Chou, P. S., Huang, B., & Ruan, W. J. (2005). Recovery from DSM-IV alcohol dependence: United States, 2001-2002. *Addiction*, *100*(3), 281–292. https://doi.org/10.1111/j.1360-0443.2004.00964.x

Dearing, R. L., Witkiewitz, K., Connors, G. J., & Walitzer, K. S. (2013). Prospective changes in alcohol use among hazardous drinkers in the absence of treatment. *Psychology of Addictive Behaviors*, *27*(1), 52–61. https://doi.org/10.1037/a0028170

Diana, M., Brodie, M., Muntoni, A., Puddu, M. C., Pillolla, G., Steffensen, S., Spiga, S., & Little, H. J. (2003). Enduring effects of chronic ethanol in the CNS: Basis for alcoholism. *Alcoholism: Clinical and Experimental Research*, *27*(2), 354–361. https://doi.org/10.1097/01.ALC.0000057121.36127.19

DiClemente, C. C., Carbonari, J. P., Montgomery, R. P. G., & Hughes, S. O. (1994). The alcohol abstinence self-efficacy scale. *Journal of Studies on Alcohol*, *55*(2), 141–148. https://doi.org/10.15288/jsa.1994.55.141

Epstein, E. E., Kahler, C. W., Mccrady, B. S., Lewis, K. D., & Lewis, S. (1995). An empirical

classification of drinking patterns among alcoholics: Binge, episodic, sporadic, and steady. *Addictive Behaviors*, *20*(1), 23–41. https://doi.org/10.1016/0306-4603(94)00043-X

Epstein, E. E., Labouvie, E., McCrady, B. S., Jensen, N. K., & Hayaki, J. (2002). A multi-site study of alcohol subtypes: Classification and overlap of unidimensional and multi-dimensional typologies. *Addiction*, *97*(8), 1041–1053. https://doi.org/10.1046/j.1360-0443.2002.00164.x

Epstein, E. E., & McCrady, B. S. (2009). Overcoming Alcohol Use Problems: A Cognitive-Behavioral Treatment Program. In *Overcoming Alcohol Use Problems: Workbook*. Oxford University Press. https://books.google.com/books?hl=en&lr=&id=bidcoAkw0n8C&oi=fnd&pg=PR11&ots=mytk7jAbYu&sig=gIngya8HJ8ElKQA_Wzh1gBbFLF0

Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods*, *41*(4), 1149–1160. https://doi.org/10.3758/BRM.41.4.1149

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*(2), 175–191. https://doi.org/10.3758/BF03193146

Glenn, S. W., & Nixon, S. J. (1996). Investigation of Cloninger's subtypes in a male alcoholic sample: Applications and implications. *Journal of Clinical Psychology*, *52*(2), 219–230. https://doi.org/10.1002/(SICI)1097-4679(199603)52:2<219::AID-JCLP13>3.0.CO;2-N

Glöckner-Rist, A., Lémenager, T., & Mann, K. (2013). Reward and relief craving tendencies in patients with alcohol use disorders: Results from the PREDICT study. *Addictive Behaviors*, *38*(2), 1532–1540. https://doi.org/10.1016/j.addbeh.2012.06.018

Goodman, L. A. (1974). Exploratory latent structure analysis using both identifiable and unidentifiable models. *Biometrika*, *61*(2), 215–231. https://doi.org/10.1093/biomet/61.2.215

Grimm, J. W., Hope, B. T., Wise, R. A., & Shaham, Y. (2001). Incubation of cocaine craving after withdrawal. *Nature*, *412*(6843), 141–142. https://doi.org/10.1038/35084134

Heinz, A., Löber, S., Georgi, A., Wrase, J., Hermann, D., Rey, E. R., Wellek, S., & Mann, K. (2003). Reward craving and withdrawal relief craving: Assessment of different motivational pathways to alcohol intake. *Alcohol and Alcoholism*, *38*(1), 35–39. https://doi.org/10.1093/alcalc/agg005

Heinz, A., Ragan, P., Jones, D. W., Hommer, D., Williams, W., Knable, M. B., Gorey, J. G., Doty, L., Geyer, C., Lee, K. S., Coppola, R., Weinberger, D. R., & Linnoila, M. (1998). Reduced central serotonin transporters in alcoholism. *American Journal of Psychiatry*, *155*(11), 1544–1549. https://doi.org/10.1176/ajp.155.11.1544

Helstrom, A. W., Blow, F. C., Slaymaker, V., Kranzler, H. R., Leong, S., & Oslin, D. (2016). Reductions in alcohol craving following naltrexone treatment for heavy drinking. *Alcohol and Alcoholism*, *51*(5), 562–566. https://doi.org/10.1093/alcalc/agw038

Herz, A. (1997). Endogenous opioid systems and alcohol addiction. *Psychopharmacology*, *129*(2), 99–111. https://doi.org/10.1007/s002130050169

Hesselbrock, V. M., & Hesselbrock, M. N. (2006). Are there empirically supported and clinically useful subtypes of alcohol dependence? *Addiction*, *101*(SUPPL. 1), 97–103. https://doi.org/10.1111/j.1360-0443.2006.01596.x

Hillemacher, T., & Bleich, S. (2008). Neurobiology and treatment in alcoholism: Recent findings regarding Lesch's typology of alcohol dependence. *Alcohol and Alcoholism*, *43*(3), 341–346. https://doi.org/10.1093/alcalc/agn016

Hunt, G. M., & Azrin, N. H. (1973). A community-reinforcement approach to alcoholism. *Behaviour Research and Therapy*, *11*(1), 91–104. https://doi.org/10.1016/0005-7967(73)90072-7

Ihssen, N., Cox, W. M., Wiggett, A., Fadardi, J. S., & Linden, D. E. J. (2011). Differentiating heavy from light drinkers by neural responses to visual alcohol cues and other motivational stimuli. *Cerebral Cortex*, *21*(6), 1408–1415. https://doi.org/10.1093/cercor/bhq220

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., Sanislow, C., & Wang, P. (2010). Research Domain Criteria (RDoC): Toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*, *167*(7), 748–751. https://doi.org/10.1176/appi.ajp.2010.09091379

Irwin, M., Schuckit, M., & Smith, T. L. (1990). Clinical importance of age at onset in type 1 and type 2 primary alcoholics. *Archives of General Psychiatry*, *47*(4), 320–324. https://doi.org/10.1001/archpsyc.1990.01810160020003

Jackson, S. E., & Chester, J. D. (2015). Personalised cancer medicine. *International Journal of Cancer*, *137*(2), 262–266. https://doi.org/10.1002/ijc.28940

Jellinek, E. M. (1960). The Disease Concept of Alcoholism. In *British Journal of Psychiatry* (Vol. 159, Issue JUL). Hillhouse Press. https://doi.org/10.1037/14090-000

Kelly, J. F. (2017). Is Alcoholics Anonymous religious, spiritual, neither? Findings from 25 years of mechanisms of behavior change research. *Addiction*, *112*(6), 929–936. https://doi.org/10.1111/add.13590

Kelly, J. F. (2019). E. M. Jellinek's disease concept of alcoholism. *Addiction*, *114*(3), 555–559. https://doi.org/10.1111/add.14400

Koob, G. F. (2010). The role of CRF and CRF-related peptides in the dark side of addiction.

Brain Research, *1314*, 3–14. https://doi.org/10.1016/j.brainres.2009.11.008

Koob, G. F., & Le Moal, M. (2001). Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*, *24*(2), 97–129. https://doi.org/10.1016/S0893-133X(00)00195-0

Koob, G. F., & Le Moal, M. (2008). Addiction and the brain antireward system. *Annual Review of Psychology*, *59*(1), 29–53. https://doi.org/10.1146/annurev.psych.59.103006.093548

Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology*, *35*(1), 217–238. https://doi.org/10.1038/npp.2009.110

Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: a neurocircuitry analysis. *The Lancet Psychiatry*, *3*(8), 760–773. https://doi.org/10.1016/S2215-0366(16)00104-8

Lane, S. P., & Sher, K. J. (2015). Limits of current approaches to diagnosis severity based on criterion counts: An example with DSM-5 alcohol use disorder. *Clinical Psychological Science*, *3*(6), 819–835. https://doi.org/https://doi.org/10.1177/2167702614553026

Lazarsfeld, P. F., & Henry, N. W. (1968). *Latent Structure Analysis*. Houghton-Mifflin.

Leggio, L., Kenna, G. A., Fenton, M., Bonenfant, E., & Swift, R. M. (2009). Typologies of alcohol dependence: From Jellinek to genetics and beyond. *Neuropsychology Review*, *19*(1), 115–129. https://doi.org/10.1007/s11065-008-9080-z

Leggio, L., Kenna, G. A., & Swift, R. M. (2008). New developments for the pharmacological treatment of alcohol withdrawal syndrome. A focus on non-benzodiazepine GABAergic medications. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *32*(5), 1106–1117. https://doi.org/10.1016/j.pnpbp.2007.09.021

Lesch, O. M., & Walter, H. (1996). Subtypes of alcoholism and their role in therapy. *Alcohol and Alcoholism*, *31*(Supplement 1), 63–67.

https://doi.org/10.1093/oxfordjournals.alcalc.a008221

Leung, H. T., & Corbit, L. H. (2017). Extinction of alcohol seeking is enhanced by compound extinction and the noradrenaline reuptake inhibitor atomoxetine. *Addiction Biology*, *22*(1), 47–57. https://doi.org/10.1111/adb.12267

Litt, M. D., Babor, T. F., DelBoca, F. K., Kadden, R. M., & Cooney, N. L. (1992). Types of alcoholics, II: Application of an empirically derived typology to treatment matching. *Archives of General Psychiatry*, *49*(8), 609–614. https://doi.org/10.1001/archpsyc.1992.01820080017003

Litten, R. Z., Egli, M., Heilig, M., Cui, C., Fertig, J., Ryan, M., Falk, D., Moss, H., Huebner, R., & Noronha, A. (2012). Medications development to treat alcohol dependence: A vision for the next decade. *Addiction Biology*, *17*(3), 513–527. https://doi.org/10.1111/j.1369-1600.2012.00454.x

Litten, R. Z., Ryan, M., Falk, D., Reilly, M., Fertig, J., & Koob, G. (2015). Heterogeneity of alcohol use disorder: Understanding mechanisms to advance personalized treatment. *Alcoholism: Clinical and Experimental Research*, *39*(4), 579–584. https://doi.org/10.1111/acer.12669

Littleton, J. (1995). Acamprosate in alcohol dependence: how does it work? *Addiction*, *90*(9), 1179–1188. https://doi.org/10.1046/j.1360-0443.1995.90911793.x

Liu, J., & Wang, L. N. (2017). Baclofen for alcohol withdrawal. *Cochrane Database of Systematic Reviews*, *2017*(8). https://doi.org/10.1002/14651858.CD008502.pub5

Lubke, G., & Neale, M. C. (2006). Distinguishing between latent classes and continuous factors: Resolution by maximum likelihood? *Multivariate Behavioral Research*, *41*(4), 499–532. https://doi.org/10.1207/s15327906mbr4104_4

Maisel, N. C., Blodgett, J. C., Wilbourne, P. L., Humphreys, K., & Finney, J. W. (2013). Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: When are these medications most helpful? *Addiction*, *108*(2), 275–293. https://doi.org/10.1111/j.1360-0443.2012.04054.x

Maisto, S. A., Conigliaro, J. C., Gordon, A. J., McGinnis, K. A., & Justice, A. C. (2008). An experimental study of the agreement of self-administration and telephone administration of the timeline followback interview. *Journal of Studies on Alcohol and Drugs*, *69*(3), 468–471. https://doi.org/10.15288/jsad.2008.69.468

Mann, K., Bladström, A., Torup, L., Gual, A., & Van Den Brink, W. (2013). Extending the treatment options in alcohol dependence: A randomized controlled study of as-needed nalmefene. *Biological Psychiatry*, *73*(8), 706–713. https://doi.org/10.1016/j.biopsych.2012.10.020

Mann, K., Kiefer, F., Smolka, M., Gann, H., Wellek, S., & Heinz, A. (2009). Searching for responders to acamprosate and naltrexone in alcoholism treatment: Rationale and design of the predict study. *Alcoholism: Clinical and Experimental Research*, *33*(4), 674–683. https://doi.org/10.1111/j.1530-0277.2008.00884.x

Mann, K., Roos, C. R., Hoffmann, S., Nakovics, H., Leménager, T., Heinz, A., & Witkiewitz, K. (2018). Precision medicine in alcohol dependence: A controlled trial testing pharmacotherapy response among reward and relief drinking phenotypes. *Neuropsychopharmacology*, *43*(4), 891–899. https://doi.org/10.1038/npp.2017.282

Mann, K., Torup, L., Sørensen, P., Gual, A., Swift, R., Walker, B., & van den Brink, W. (2016). Nalmefene for the management of alcohol dependence: review on its pharmacology, mechanism of action and meta-analysis on its clinical efficacy. *European*

Neuropsychopharmacology, *26*(12), 1941–1949. https://doi.org/10.1016/j.euroneuro.2016.10.008

Miller, W. R., & Del Boca, F. K. (1994). Measurement of drinking behavior using the Form 90 family of instruments. *Journal of Studies on Alcohol*, *55*(SUPPL. 12), 112–118. https://doi.org/10.15288/jsas.1994.s12.112

Miller, W. R., & Rollnick, S. (2012). *Motivational Interviewing: Helping People Change* (3rd ed.). The Guilford Press. https://www.guilford.com/books/Motivational-Interviewing/Miller-Rollnick/9781609182274

Miller, W. R., Tonigan, J. S., & Longabaugh, R. (1995). The Drinker Inventory of Consequences (DrInC). An Instrument for Assessing Adverse Consequences of Alcohol Abuse. Test Manual. In *Project MATCH Monograph Series* (Volume 4, Vol. 4). National Institute on Alcohol Abuse and Alcoholism. http://pubs.niaaa.nih.gov/publications/drinc.pdf

Moss, H. B., Chen, C. M., & Yi, H. Y. (2007). Subtypes of alcohol dependence in a nationally representative sample. *Drug and Alcohol Dependence*, *91*(2–3), 149–158. https://doi.org/10.1016/j.drugalcdep.2007.05.016

Moss, H. B., Chen, C. M., & Yi, H. Y. (2008). DSM-IV criteria endorsement patterns in alcohol dependence: Relationship to severity. *Alcoholism: Clinical and Experimental Research*, *32*(2), 306–313. https://doi.org/10.1111/j.1530-0277.2007.00582.x

Moss, H. B., Chen, C. M., & Yi, H. Y. (2010). Prospective follow-up of empirically derived alcohol dependence subtypes in wave 2 of the national epidemiologic survey on alcohol and related conditions (NESARC): Recovery status, alcohol use disorders and diagnostic criteria, alcohol consumption behavio. *Alcoholism: Clinical and Experimental Research*, *34*(6), 1073–1083. https://doi.org/10.1111/j.1530-0277.2010.01183.x

Nylund-Gibson, K., Grimm, R. P., & Masyn, K. E. (2019). Prediction from latent classes: A demonstration of different approaches to include distal outcomes in mixture models. *Structural Equation Modeling: A Multidisciplinary Journal*, *26*(6), 967–985. https://doi.org/10.1080/10705511.2019.1590146

Nylund, K. L., Asparouhov, T., & Muthén, B. O. (2007). Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. *Structural Equation Modeling*, *14*(4), 535–569. https://doi.org/10.1080/10705510701793320

Ooteman, W., Koeter, M., Verheul, R., Schippers, G., & Van den Brink, W. (2006). Development and validation of the Amsterdam motives for drinking scale (AMDS): An attepmt to distinguish relief and reward drinkers. *Alcohol and Alcoholism*, *41*(3), 284–292. https://doi.org/10.1093/alcalc/agl012

Pedersen, E. R., Grow, J., Duncan, S., Neighbors, C., & Larimer, M. E. (2012). Concurrent validity of an online version of the timeline followback assessment. *Psychology of Addictive Behaviors*, *26*(3), 672–677. https://doi.org/10.1037/a0027945

Pettinati, H. M., Dundon, W., & Lipkin, C. (2004). Gender differences in response to sertraline pharmacotherapy in type A alcohol dependence. *American Journal on Addictions*, *13*(3), 236–247. https://doi.org/10.1080/10550490490459906

Pombo, S., Da Costa, N. F., Figueira, M. L., Ismail, F., & Lesch, O. M. (2015). Multidimensional alcoholism typologies: Could they guide clinical practice? Results from a 3-month prospective study. *International Journal of Psychiatry in Clinical Practice*, *19*(2), 137–147. https://doi.org/10.3109/13651501.2015.1016972

Project MATCH Research Group. (1993). Project MATCH: Rationale and methods for a

multisite clinical trial matching patients to alcoholism treatment. *Alcoholism: Clinical and Experimental Research*, *17*(6), 1130–1145. https://doi.org/10.1111/j.1530-0277.1993.tb05219.x

Project MATCH Research Group. (1997). Matching alcoholism treatments to client heterogeneity: Project MATCH posttreatment drinking outcomes. *Journal of Studies on Alcohol*, *58*(1), 7–29. https://doi.org/10.15288/jsa.1997.58.7

Ray, L. A., Bujarski, S., Grodin, E., Hartwell, E., Green, R. J., Venegas, A., Lim, A. C., Gillis, A., & Miotto, K. (2019). State-of-the-art behavioral and pharmacological treatments for alcohol use disorder. *American Journal of Drug and Alcohol Abuse*, *45*(2), 124–140. https://doi.org/10.1080/00952990.2018.1528265

Ray, L. A., Chin, P., & Miotto, K. (2012). Naltrexone for the Treatment of Alcoholism: Clinical Findings, Mechanisms of Action, and Pharmacogenetics. *CNS & Neurological Disorders - Drug Targets*, *9*(1), 13–22. https://doi.org/10.2174/187152710790966704

Ribeiro, M. S., Ribeiro, L. C., & Ferreira, R. A. (2015). A possible contribution to improving the therapeutic potentials of Babor's typology of alcohol dependent patients. *Jornal Brasileiro de Psiquiatria*, *64*(3), 200–206. https://doi.org/10.1590/0047-2085000000079

Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Research Reviews*, *18*(3), 247–291. https://doi.org/10.1016/0165-0173(93)90013-P

Roos, C. R., Mann, K., & Witkiewitz, K. (2017). Reward and relief dimensions of temptation to drink: Construct validity and role in predicting differential benefit from acamprosate and naltrexone. *Addiction Biology*, *22*(6), 1528–1539. https://doi.org/10.1111/adb.12427

Sacks, J. J., Gonzales, K. R., Bouchery, E. E., Tomedi, L. E., & Brewer, R. D. (2015). 2010

National and state costs of excessive alcohol consumption. *American Journal of Preventive Medicine*, *49*(5), e73–e79. https://doi.org/10.1016/j.amepre.2015.05.031

Samochowiec, J., Kucharska-Mazur, J., Grzywacz, A., Pelka-Wysiecka, J., Mak, M., Samochowiec, A., & Bienkowski, P. (2008). Genetics of Lesch's typology of alcoholism. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *32*(2), 423–427. https://doi.org/10.1016/j.pnpbp.2007.09.013

Sannibale, C., & Hall, W. (1998). An evaluation of Cloninger's typology of alcohol abuse. *Addiction*, *93*(8), 1241–1249. https://doi.org/10.1046/j.1360-0443.1998.938124112.x

Satorra, A., & Bentler, P. M. (2010). Ensuring positiveness of the scaled difference chi-square test statistic. *Psychometrika*, *75*(2), 243–248. https://doi.org/10.1007/s11336-009-9135-y

Schacht, J. P., Anton, R. F., & Myrick, H. (2013). Functional neuroimaging studies of alcohol cue reactivity: A quantitative meta-analysis and systematic review. *Addiction Biology*, *18*(1), 121–133. https://doi.org/10.1111/j.1369-1600.2012.00464.x

Schlaff, G., Walter, H., & Lesch, O. M. (2011). The Lesch alcoholism typology: Psychiatric and psychosocial treatment approaches. *Annals of Gastroenterology*, *24*(2), 89–97. http://www.ncbi.nlm.nih.gov/pubmed/24713718

Schuckit, M. A., Tipp, J. E., Smith, T. L., Shapiro, E., Hesselbrock, V. M., Bucholz, K. K., Reich, T., & Nurnberger, J. I. (1995). An evaluation of Type A and B alcoholics. *Addiction*, *90*(9), 1189–1203. https://doi.org/10.1046/j.1360-0443.1995.90911894.x

Sigvardsson, S., Bohman, M., & Cloninger, C. R. (1996). Replication of the Stockholm adoption study of alcoholism: Confirmatory cross-fostering analysis. *Archives of General Psychiatry*, *53*(8), 681–687. https://doi.org/10.1001/archpsyc.1996.01830080033007

Simpson, S., Shankar, K., Kimbrough, A., & George, O. (2020). Role of Corticotropin-Releasing

Factor in Alcohol and Nicotine Addiction. *Brain Research*, *1740*, 146850. https://doi.org/10.1016/J.BRAINRES.2020.146850

Sobell, L. C., Agrawal, S., Sobell, M. B., Leo, G. I., Young, L. J., Cunningham, J. A., & Simco, E. R. (2003). Comparison of a Quick Drinking Screen with the Timeline Followback for Individuals with Alcohol Problems. *Journal of Studies on Alcohol*, *64*(6), 858–861. https://doi.org/10.15288/jsa.2003.64.858

Sobell, L. C., Brown, J., Leo, G. I., & Sobell, M. B. (1996). The reliability of the Alcohol Timeline Followback when administered by telephone and by computer. *Drug and Alcohol Dependence*, *42*(1), 49–54. https://doi.org/10.1016/0376-8716(96)01263-X

Sobell, L. C., & Sobell, M. B. (1992). Timeline follow-back: A technique for assessing self-reported alcohol consumption. In R. Z. Litten & J. P. Allen (Eds.), *Measuring Alcohol Consumption: Psychosocial and Biochemical Methods* (pp. 41–72). Humana Press. https://doi.org/10.1007/978-1-4612-0357-5_3

Solomon, R. L., & Corbit, J. D. (1974). An opponent-process theory of motivation: I. Temporal dynamics of affect. *Psychological Review*, *81*(2), 119–145. https://doi.org/10.1037/h0036128

Spanagel, R. (2017). Animal models of addiction. *Dialogues in Clinical Neuroscience*, *19*(3), 247–258. https://doi.org/10.1093/med/9780199934959.003.0050

Spanagel, R., & Weiss, F. (1999). The dopamine hypothesis of reward: Past and current status. *Trends in Neurosciences*, *22*(11), 521–527. https://doi.org/10.1016/S0166-2236(99)01447-2

Spanagel, R., & Zieglglnsberger, W. (1997). Anti-craving compounds for ethanol: New pharmacological tools to study addictive processes. *Trends in Pharmacological Sciences*, *18*(2), 54–59.

Steffensen, S. C., Walton, C. H., Hansen, D. M., Yorgason, J. T., Gallegos, R. A., & Criado, J. R. (2009). Contingent and non-contingent effects of low-dose ethanol on GABA neuron activity in the ventral tegmental area. *Pharmacology Biochemistry and Behavior*, *92*(1), 68–75. https://doi.org/10.1016/j.pbb.2008.10.012

Stewart, J., & Vezina, P. (1988). A comparison of the effects of intra-accumbens injections of amphetamine and morphine on reinstatement of heroin intravenous self-administration behavior. *Brain Research*, *457*(2), 287–294. https://doi.org/10.1016/0006-8993(88)90698-1

Štimac, D., & Franjić, N. (2016). Personalized Medicine in Gastroenterology. In N. Bodiroga-Vukobrat, D. Rukavina, K. Pavelić, & G. Sander (Eds.), *Personalized Medicine: Europeanization and Globalization* (pp. 257–264). Springer, Cham. https://doi.org/10.1007/978-3-319-39349-0_13

Storvik, M., Haukijärvi, T., Tupala, E., & Tiihonen, J. (2008). Correlation between the SERT binding densities in hypothalamus and amygdala in Cloninger type 1 and 2 alcoholics. *Alcohol and Alcoholism*, *43*(1), 25–30. https://doi.org/10.1093/alcalc/agm157

Substance Abuse and Mental Health Services Administration (SAMHSA). (2018). *Section 5 PE Tables – Results from the 2018 National Survey on Drug Use and Health: Detailed Tables, Sections 1 - 3, SAMHSA, CBHSQ*. https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2018R2/NSDUHDetTabsSect5pe2018.htm#tab5-4b

Tawa, E. A., Hall, S. D., & Lohoff, F. W. (2016). Overview of the genetics of alcohol use disorder. *Alcohol and Alcoholism*, *51*(5), 507–514. https://doi.org/10.1093/alcalc/agw046

Tiihonen, J., Kuikka, J., Bergström, K., Hakola, P., Karhu, J., Ryynänen, O. P., & Föhr, J. (1995). Altered striatal dopamine re-uptake site densities in habitually violent and non-violent alcoholics. *Nature Medicine*, *1*(7), 654–657. https://doi.org/10.1038/nm0795-654

Tucker, J. A., Chandler, S. D., & Witkiewitz, K. (2020). Epidemiology of recovery from alcohol use disorder. *Alcohol Research: Current Reviews*, *40*(3), 1–12. https://doi.org/10.35946/arcr.v40.3.02

Tupala, E., Hall, H., Bergström, K., Mantere, T., Räsänen, P., Särkioja, T., Hiltunen, J., & Tiihonen, J. (2003). Different effect of age on dopamine transporters in the dorsal and ventral striatum of controls and alcoholics. *Synapse*, *48*(4), 205–211. https://doi.org/10.1002/syn.10206

Venniro, M., Caprioli, D., & Shaham, Y. (2016). Animal models of drug relapse and craving: From drug priming-induced reinstatement to incubation of craving after voluntary abstinence. *Progress in Brain Research*, *224*, 25–52. https://doi.org/10.1016/bs.pbr.2015.08.004

Verheul, R., Van Den Brink, W., & Geerlings, P. (1999). A three-pathway psychobiological model of craving for alcohol. *Alcohol and Alcoholism*, *34*(2), 197–222. https://doi.org/10.1093/alcalc/34.2.197

Von Knorring, L., Palm, U., & Andersson, H. E. (1985). Relationship between treatment outcome and subtype of alcoholism in men. *Journal of Studies on Alcohol*, *46*(5), 388–391. https://doi.org/10.15288/jsa.1985.46.388

Walter, H., Ramskogler-Skala, K., Dvorak, A., Gutierrez-Lobos, K., Hartl, D., Hertling, I., Munda, P., Thau, K., Lech, O. M., & De Whitte, P. (2006). Glutamic acid in withdrawal and weaning in patients classified according to Cloninger's and Lesch's typologies. *Alcohol and Alcoholism*, *41*(5), 505–511. https://doi.org/10.1093/alcalc/agl042

Weinland, C., Braun, B., Mühle, C., Kornhuber, J., & Lenz, B. (2017). Cloninger type 2 score and Lesch typology predict hospital readmission of female and male alcohol-dependent

inpatients during a 24-month follow-up. *Alcoholism: Clinical and Experimental Research*, *41*(10), 1760–1767. https://doi.org/10.1111/acer.13468

Weiss, F., Parsons, L. H., Schulteis, G., Hyytiä, P., Lorang, M. T., Bloom, F. E., & Koob, G. F. (1996). Ethanol self-administration restores withdrawal-associated deficiencies in accumbal dopamine and 5-hydroxytryptamine release in dependent rats. *Journal of Neuroscience*, *16*(10), 3474–3485. https://doi.org/10.1523/jneurosci.16-10-03474.1996

Witkiewitz, K., Roos, C. R., Mann, K., & Kranzler, H. R. (2019). Advancing precision medicine for alcohol use disorder: Replication and extension of reward drinking as a predictor of naltrexone response. *Alcoholism: Clinical and Experimental Research*, *43*(11), 2395–2405. https://doi.org/10.1111/acer.14183

Yoshino, A., Kato, M., Takeuchi, M., Ono, Y., & Kitamura, T. (1994). Examination of the tridimensional personality hypothesis of alcoholism using empirically multivariate typology. *Alcoholism: Clinical and Experimental Research*, *18*(5), 1121–1124. https://doi.org/10.1111/j.1530-0277.1994.tb00091.x

Young, J. P., Achtmeyer, C. E., Bensley, K. M., Hawkins, E. J., & Williams, E. C. (2018). Differences in perceptions of and practices regarding treatment of alcohol use disorders among VA primary care providers in urban and rural clinics. *Journal of Rural Health*, *34*(4), 359–368. https://doi.org/10.1111/jrh.12293