

Predictors of relapse in alcohol use disorder: Identifying individuals most vulnerable to relapse

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Abstract

This paper reviews the literature discussing the various biological, psychological, environmental, and social factors contributing to the risk of relapse for individuals with Alcohol Use Disorder (AUD). Identifying these risk factors and understanding their complex interactions in contributing to relapse vulnerability is crucial to improving relapse prevention interventions and outcomes. The impact of chronic alcohol abuse on brain structure and function are discussed. Specifically, altered reward circuitry, modified stress pathways, and compromised frontal white matter integrity in regions associated with decision making, impulse control, and executive functioning are identified as risk factors associated with predicting long-term abstinence. Neural adaptations increased craving, which has been attributed to relapse vulnerability. The literature examined alcohol attentional-bias, coping style, early onset alcohol dependence, duration of treatment, attendance at AA, personality traits, self-efficacy, comorbid depression, deficits in social cognition, interpersonal relationships, and facial emotion recognition ability as risk factors that may be predictive of relapse. Clinicians should encourage AA attendance, treat depressive symptoms, address coping mechanisms, and enhance social support in the first year of abstinence. Future studies that focus on establishing the strength of the predictability of these risk factors, as well as identifying protective factors, could make substantive contributions to improving outcomes for individuals who are most vulnerable to the relapse process. Identifying risk factors at the brain and biological level could establish biomarkers for relapse risk, which would have implications for clinical practice and treatment of AUD by enhancing targeted interventions and individualized care.

Alcohol Use Disorder (AUD) is described as a chronic relapsing condition with definitive behavioral markers and is characterized by repeated drug intake despite severe negative consequences [1]. With 12-month prevalence rates at 14% and lifetime estimates of 29% [2], it is clear that AUD adversely and substantially affects individual and societal health [3]. Recognized clinically as affecting decision making, relationships, and neurological function [4], AUD has been a major cause of personal, family, and social conflict for centuries [2]. Behavioral change is difficult to achieve and relapse after detoxification is common, especially when AUD individuals are exposed to alcohol-associated cues or stress [5].

Alcohol relapse is defined as the process of returning to heavy drinking after a period of abstinence or reduced use and is typically characterized by 4+ drinks for women and 5+ drinks for men [6]. Nearly all models of the relapse process suggest an interaction between biological, psychological, environmental and social factors and emphasize stable risk factors generating greater relapse vulnerability in the presence of immediate risk factors. Comprehensive efforts to identify relevant risk factors is of crucial importance in order to improve relapse prevention interventions [6].

Relapse prevention was developed as an approach to the treatment of AUD by Alan Marlatt and colleagues in the 1970s, and its efficacy has been shown repeatedly since [7]. While past disease models have described a linear path towards relapse, a new model illustrating the multiple processes of internal and external, situational and constant, and changing vulnerabilities that put an individual at high relapse risk has been proposed [7]. The severity of clinical presentation is associated with poorer treatment outcomes [4], but the complex interplay of variables contributing to relapse risk may

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change dynamically during and after treatment [8]. Environmental factors contributing to relapse have been well established, but the underlying psychological and neurobiological mechanism on which those factors act are inadequately understood at this time [5]. Information on relapse susceptibility has significant implications for clinical practice and treatment of AUD, especially with advancement of targeted interventions and innovative brain and biology related measures of risk that could serve as biomarkers to identify those most vulnerable to relapse [9]. Therefore, protective factors against relapse of this chronic brain disease should be studied and individuals most vulnerable should be assessed [3]. This paper will discuss the various biological, psychological, environmental, and social factors that have potential use for identification of individuals with highest risk of relapse in AUD.

As a result of the reinforcing attributes of substance use, AUD is thought to involve modifications of reward circuitry [10]. Thus, a substantial amount of AUD neurobiological research has focused on alcohol-related activation and long-term adaptations in the mesocortical dopaminergic reward pathways [11]. Neuroimaging studies suggest that chronic alcohol abuse (CAA) reduces dopamine receptors in striatal regions and frontal lobe dopamine transmission up to 4 months after abstinence [9]. Relapse is associated with “enhanced dopamine levels in the medial prefrontal cortex and mesolimbic system with an inverse correlation between β oscillatory activity and dopamine availability in the nucleus accumbens (NAcc) shell” [12]. This data indicates synchronous oscillatory activity of the local neural population in the NAcc shell during a relapse situation, which is presumably pertinent to dopaminergic medium spiny neurons that show the same pattern [12]. It is proposed that these alterations in neuronal network activity, particularly in the reward pathway, accompany or even mediate relapse behavior [12].

Conditioned rewards (e.g. alcohol-associated cues) mediated by limbic connections among the ventral tegmental area (VTA), NAcc, and the amygdala are potentiated by drug use [10]. Concurrent dysregulation in frontal circuits involved in outcome appraisal, response inhibition, and cognitive control contribute to persisted substance use despite adverse health and social outcomes [10]. CAA also elevates estrogen in both men and women. Estrogen modulates dopamine activity in the striatum and NAcc and is associated with higher levels of cortisol, which consequently may increase vulnerability to relapse [11].

Recent evidence has suggested a disordered reward-based impulsivity in AUD, which may be both a causative factor and consequence of the disorder [13]. “Impulsive choice” refers to “an increased preference for smaller immediate rewards over larger delayed rewards, to the detriment of long-term outcomes,” and is typically assessed with delayed discounting tasks [14]. An individual may have a predisposition to impulsivity and CAA may cause brain function abnormalities that further exacerbate this predisposition [13]. Therefore, heightened impulsivity may result in a vicious cycle with shorter abstinence, reduced likelihood of treatment success, and greater likelihood of relapse [14]. Neurocognitive impulsivity mediated by frontostriatal circuits plays a critical role in the development and maintenance of addictive behavior and appears sensitive for the prediction of relapse [14].

Functional magnetic resonance imaging and positron emission tomography data suggest that compulsions to use drugs involve

regions comprising aspects of the extended reward system, including the ventral striatum (VS), insula, orbitofrontal cortex, and lateral prefrontal cortex [13]. The VS signals the likelihood of reward and may cause disordered neural signaling of alcohol versus nonalcohol reward availability that may drive impulsive alcohol use behavior in clinical samples [13]. Impulsive behaviors may also be due to hyperactivity within the basal ganglia reward and habit-forming system and prefrontal components exerting inhibitory control [14].

Poorer response inhibition and an inclination toward steeper discounting of delayed rewards should be observed as neurocognitive risk factors that can be identified early in the course of AUD treatment [14]. Altered delay discounting has been suggested as a behavioral marker for addiction [15], and targeting response inhibition and delay discounting has potential to increase periods of abstinence and reduce the probability of relapse [14]. Additionally, AUD patients typically show greater engagement of motor response circuits preceding inhibition trials, suggesting greater pre-potent tendencies that may prompt disinhibition [16]. Thus, “AUD severity is related to neural response during response inhibition and causal mechanisms responsible for impaired inhibitory control. More severe AUDs are associated with reduced engagement of neural circuits involved in behavioral control and enhanced pre-potent responding” [16]. The progression and relapse of AUD may be affected by this altered control [16].

The neuroadaptive modifications in reward circuitry may also be responsible for reduction of frontal white matter integrity in AUD patients. Relapsers have significantly lower frontal white matter integrity than abstainers in regions associated with decision making, impulse control, and executive functioning [10]. Individuals with compromised frontal white matter integrity struggled to sustain treatment gains when compared to individuals with robust white matter, who continued to see gains 6 months after the start of treatment [10]. Additionally, low levels of brain metabolites N-acetylaspartate (NAA) and Choline (Cho) were observed in frontal white matter and thalamus of relapsers relative to alcoholics who maintained 3-month sobriety and controls, which corresponds with findings that high levels of NAA in these regions is associated with longer abstinence [17]. Current neurobiological models of AUD processes that emphasize reduced frontal lobe mediated cognitive control and heightened reward sensitivity coincide with the pattern of suboptimal microstructural frontal integrity observed in relapsing individuals [10]. Thus, frontal white matter integrity and NAA/Cho levels within frontal white matter and thalamus may represent biomarkers that indicate the need for a particular treatment [10]. These neural adaptations matter because they may cause subsequent disrupted prefrontal cortex function and associated lack of top-down inhibition, causing increased craving and relapse in newly abstinent patients [11].

Craving and relapse are two core features of AUD [11]. Craving can be defined as “a multifaceted phenomenon that incorporates the appetite drive for reward, the need for reduction of associated physiological distress, and a compulsive motivational state characterized by strong intent with or without loss of control” [11]. Colloquially, craving is described by a powerful urge or abnormal longing and is often cited by those with AUD as the reason for relapse [11]. Individuals who reported an increase in

cravings on a given prompt compared to those who did not were 14 times more likely to report relapse on the subsequent prompt [18]. Neuroadaptations from CAA are vital in understanding mechanisms that increase craving in pathological drug seeking behavior and how these changes increase the likelihood of relapse [19]. The alteration of dopaminergic signaling previously discussed, particularly in the VS and VTA, is associated with increased craving and self-administration in laboratory animals [9]. Studies have shown interactions between AUD corticolimbic connectivity and craving and establish an explanatory relationship between network connectivity and dynamic risk factors that contribute to relapse [19]. Results demonstrate that “relapse vulnerability is attributed to craving dysregulation manifested by enhanced connectivity in striatolimbic regions and diminished corticostriatal connectivity” [19]. Additionally, elevated glutamate levels in the left dorsolateral prefrontal cortex (LDLPFC) are associated with craving intensity and further study should be done to evaluate the merits of glutamate spectroscopy as a biological correlate of craving intensity [20].

Evidence indicates that the neural circuits involved in drug reward extensively overlap with the brain systems involved in stress and emotions. In addition to reward pathway alterations, CAA neuroadaptations can change brain stress systems and are associated with heightened activity in the stress pathways [9]. Some of these changes include increased secretion of the stress hormones corticotropin-releasing factor (CRF), norepinephrine, and cortisol in various stress and emotion centers, including the hypothalamus, amygdala, hippocampus, and prefrontal regions [9]. These changes cause an increase in stress-related symptoms such as increased anxiety and negative emotions, changes in sleep and appetite, aggressive behaviors, changes in attention, concentration, memory, and craving [9].

Psychobiological and neuroimaging research points to CAA changes in brain volume, function, and stress response which contribute to higher craving and increased relapse risk [9]. AUD disrupts normal functioning in the HPA axis and autonomic components of peripheral stress pathways, which mobilize the body for action during stress and are involved in physiological regulation of the stress response [9]. Risk of relapse is increased by HPG axis dysregulation, as neuroactive steroids that counteract HPA axis activation increase during intoxication and contribute to the blunted response of the HPA axis to alcohol and stress seen in AUD [11]. These neuroactive steroid levels have been shown to increase during binge intoxication and then decrease significantly during withdrawal. Results have indicated that elevated morning cortisol to ACTH ratios, which measure sensitivity of the adrenal glands in response to the ACTH signal, more than doubled the risk of future relapse [11]. Due to the blunted cortisol response to stress seen in AUD, targeting HPA axis pathophysiology is vital because compounds that suppress the HPA axis will suppress both tonic cortisol (basal) and blunted cortisol responses (phasic), a response associated with heightened relapse risk and alcohol intake [21].

In the clinical context, “AUD patients entering outpatient treatment report high levels of stress and an inability to manage distress adaptively, thereby increasing the risk of succumbing to high levels of craving and relapse” [9]. Relapse rates remain high despite learning cognitive-behavioral strategies in treatment, which suggests difficulties experienced in applying and accessing strategies in real-world relapse situations [9]. Development of treatment strategies that

help normalize the stress response, such as medications targeting the stress pathways, may be helpful in decreasing craving and improving relapse outcomes. Novel medications blocking CRF, noradrenergic, and GABAergic agents are currently being tested to assess their efficacy in stress-related relapse. CAA stress system adaptations can also be seen by increased physiological arousal as measured by heart rate and decreased heart rate variability, which serves as a measure of parasympathetic function [9]. Data suggests cue-elicited high-frequency heart rate variability and alcohol attentional-bias (AB) can forecast relapse and might be used as prognostic indicators for relapse indices in a clinical context [22].

AB during detoxification has previously been shown to predict relapse, and recent evidence suggests that AB to positive change-related words are a better predictor for treatment outcome than alcohol-related or negative change-related words [23]. Recently detoxified patients may be vulnerable to addiction-related cues that exist outside directed attention, which bypass intentional control processes [24]. Sensitivity of occipital event-related potentials to alcohol-related stimuli may be an indicator of abstinence success in recently detoxified patients [24].

A strong link between AUD chronicity and social cognition has been well established and cumulative neurotoxic effects of CAA patterns may be recognized by problems with emotional understanding, empathy, apathy, and social inhibition [4]. Social skills, social support, and interpersonal relationships are particularly indicative of long-term abstinence and are crucial to recovery [4]. Decoding deficits of emotional facial expressions and reduced prefrontal and limbic activation during emotional face processing in AUD patients have been reported by abstract neuropsychological and imaging studies [25]. Significantly poorer facial emotion recognition ability at treatment onset has been found in relapsers than abstainers, so clinicians should treat impaired facial emotion recognition as a neurocognitive risk factor [26].

AUD patients present with reduced activation toward aversive faces-neutral shapes in bilateral fusiform gyrus, right middle frontal gyrus, right inferior parietal gyrus, and left cerebellum when compared with controls [25]. High activation in the left rostral anterior cingulate cortex (ACC) elicited by affective faces was significantly correlated with longer abstinence and may be a resilience factor used to predict treatment outcome [25]. However, ACC integrity may be compromised in AUD patients with high lifetime drinking history (LDH) due to neurotoxic effects. LDH is correlated with worse performance on tasks including facial stimuli and inefficient compensatory mechanisms may be observed by elevated activation in the fusiform ‘face’ area [25]. Additionally, data found that AUD patients generated significantly fewer socially sensitive and practically effective solutions for problematic interpersonal situations than the control group and had significantly more problems interpreting sarcastic remarks in difficult interpersonal situations [27]. Therapeutic interventions such as emotion evaluation training may facilitate coping with social stress and reduce relapses after detoxification and specific impairment patterns should be addressed when treating impaired social skills in AUD patients [25,27].

An individual’s coping style may have significant implications for outcome success [18]. Hope or belief that recovery is possible is a vital cognitive construct preceding behavioral activation that has been associated with relapse [3]. When experiencing an increase in cravings, individuals who used acceptance coping styles were likely

to have decreased risk for relapse, while those who used distraction and disengagement coping styles demonstrated increased risk [18]. Levels of healthy coping skills in response to alcohol cues have positively correlated with activation in the right dorsomedial prefrontal cortex (DMPFC) and may reflect greater action restraint and top-down PFC control processing, which in turn may protect against relapse [3].

Social network behavior therapy is one type of behavioral intervention for AUD and is particularly useful for preventing alcohol use in response to physical pain and negative affect [6]. Data suggests that negative affect significantly mediates the association between pain and drinking outcomes, and therefore negative affect-mediated pain may be an essential risk factor in the relapse process [6]. Reported pain levels at the end of treatment significantly predicted drinking frequency and intensity at 12 months posttreatment, so it may be important to assess for level of pain as a predictive ultimate drinking outcome. Evidence suggests that interventions to reduce negative affect may be especially vital among AUD patients with chronic pain [6].

Physical pain is not the only type of pain associated with relapse. AUD patients with comorbid depression may be more likely to relapse and present with various problems in psychosocial functioning [28]. In a study of clinical predictors of AUD relapse during recurrence of major depression, twenty-six percent of patients relapsed and relapsers were more likely to be male, single, less educated, and younger than abstainers [29]. Individuals were significantly more likely to relapse if they experienced early onset alcohol dependence or past year drug use, and early onset AUD was a more powerful predictor of relapse than early onset major depression [29]. However, a different study found that clinically significant depressive symptoms at treatment admission were found to be significantly related to alcohol use at 1-year follow up [28]. A significant decrease of depression severity was associated with longer abstinence duration, suggesting that clinically significant depressive symptoms at the start and end of treatment could be a predictor of poor treatment outcomes [28]. Additional analyses among relapsers indicated that smokers and individuals with a comorbid medical condition relapsed earlier after detoxification [8]. Therefore, better treatment outcomes may follow effective treatment of depressive disorders and smoking cessation interventions that are concurrent with AUD-focused interventions [8].

Previous studies have also examined personality traits as predictors of relapse, finding that patients who were both low in conscientiousness and high in neuroticism had the greatest risk of returning to drinking [29]. Self-efficacy is a powerful predictor of short- and long-term remission and numerous variables predicted self-efficacy at 1 year [30]. These variables included "improvement from baseline to 1 year in heavy drinking, alcohol-related problems, impulsivity, avoidance coping, social support from friends, and long duration of participation in Alcoholics Anonymous (AA)" [30]. Improvement in self-efficacy over 16 years was anticipated by female gender, more education, and impulsivity during the first year [30]. Reduced modifiable risk factors and likelihood of remission were predicted by longer duration of treatment and attendance at AA in the first year, which was shown to increase remission more among high-risk than among low-risk individuals [31].

Individuals who did not obtain help were less likely to achieve 3-year remission and more likely to relapse [32]. 3-year remission

was best predicted by less alcohol consumption and fewer drinking problems, more self-efficacy and less reliance on avoidance coping, particularly for AUD individuals who remitted without treatment [32]. This suggests that natural remission may be followed by a high likelihood of relapse. Among patients who re-entered treatment at 3 years, those who had less self-efficacy, relied on avoidance coping, and were less likely to see heavy drinking as a problem were more likely to relapse by 16 years [32].

AUD is a serious and chronic brain disease that causes substantial alterations in various biological, psychological, and psychosocial functioning [8]. The chronic relapsing-remitting course of AUD is easily recognized in clinical populations by the 40-60% of patients who relapse within 3 months posttreatment and 70-80% who relapse by 12 months [33]. Relapse prevention seeks to determine high-risk variables which increase vulnerability to relapse and protective factors should be studied to enhance successful treatment outcomes [3]. The numerous variables that predict relapse discussed in this paper are substantially linked and should be treated as so. A summary of specific predictive variables and connections that link them is included in the final section of this paper.

Modifications of reward circuitry as seen by enhanced regional dopamine levels is predictive of relapse [10]. Subsequent disordered reward-based impulsivity and prefrontal components exerting inhibitory control are linked to reduced frontal white matter integrity and NAA/Cho levels. This relationship is partially responsible for prefrontal dysregulation and resulting disinhibition, a significant variable associated with poor treatment outcomes [10,26]. Alterations in the dopaminergic signaling mentioned as a significant disruption in reward pathways has been shown to increase craving, along with elevated glutamate levels in the LDLPFC [5,9,20,]. Craving is often cited by AUD patients as the reason for relapse and is additionally increased by stress exposure [5,11]. Stress responsivity in AUD patients demonstrates altered stress pathways and can be observed by increased secretion of stress hormones (e.g. cortisol), disruption of the HPA axis, and decreased heart rate variability [9]. There is significant overlap between stress and reward systems, so the craving outcome by both variables is easily understood [9]. The disrupted prefrontal cortex activity previously mentioned mediates the relationship between adrenal sensitivity and relapse risk, which creates a link between reduced frontal white matter integrity and stress [11]. Essentially, brain volume, function, and stress response altered by CAA contributes to higher craving and increased relapse risk [9].

Other variables that predict alcohol relapse are alcohol attentional-bias, problems with social cognition and interpersonal relationships, and facial emotion recognition ability exhibited by AUD patients [4,22,26]. Individuals with comorbid depression are less likely to maintain abstinence and more likely to present with problems in psychosocial functioning [28]. Negative mood is associated with increased craving, which is presumably partially responsible for heightened vulnerability to relapse in depressed AUD patients [9]. Negative affect-mediated physical pain and distraction and disengagement versus acceptance coping styles increase likelihood of relapse [6,18]. Hope or belief that recovery is possible is associated with better treatment outcomes, along with duration of treatment and attendance at AA [3,31]. Individuals with personality traits including low conscientiousness and high neuroticism are more likely to relapse and self-efficacy is a powerful predictor of

short- and long-term abstinence [29,30]. Variables that predict self-efficacy include impulsivity, avoidance coping, social support, and duration in AA [30]. Severity of clinical presentation is associated with probability of relapse, as is male gender, less education, single status, and younger age [4,29].

In conclusion, comprehensive evidence indicates that CAA is associated with changes in emotion, stress, and motivational pathways which may influence alcohol relapse risk [9]. Clinicians should encourage AA attendance, treat depressive symptoms, address coping mechanisms, and enhance social support in the first year of abstinence. Monitoring individuals whose alcohol problems and impulsivity improve unusually quickly may be vital in determining at-risk patients [30]. These components of treatment are crucial to outcome success, and the various other factors discussed in this paper may serve as quantifiable markers for AUD relapse after remission. The predictive efficacy of these interactive variables may help identify individuals most vulnerable to alcohol relapse.

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