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Indexing the “dark side of addiction”: Substance-induced affective symptoms and alcohol use disorders

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Abstract

Background: The emergence of negative affective symptoms over the course of alcohol use disorders (AUDs) (e.g. “dark side symptoms”) has been suggested theoretically, however, the description of their occurrence is limited.

Aims: This study operationalized 2 negative affect symptoms and tested the strength of association between these phenotypes and 1) indicators of the clinical course of the severity of AUD, 2) comorbid Axis I psychiatric disorders, suicidal behaviors, and trait neuroticism, 3) whether participants reported drinking to relieve the negative affective symptoms.

Design: A retrospective cross-sectional study was used to evaluate associations, using logistic regression, between the two negative affective symptoms and clinical measures of AUD severity and progression as well as comorbidity with other psychiatric disorders and conditions, adjusted for demographic characteristics.

Setting: U.S. community based studies.

Participants: 2,568 individuals with AUDs obtained from larger population studies that targeted individuals of European (n=1663), Mexican and American Indian (n=905) ancestry.

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Declaration of interests:

The authors report no conflicts of interest.

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Measurements: Semi-Structured Assessment for the Genetics of Alcoholism was used to ascertain: the 2 “dark side” phenotypes, clinical diagnoses, the clinical course of AUD, and associated symptoms.

Findings: The two phenotypes were: 1) being anxious or depressed when trying to cut down or stop drinking and 2) experiencing disabling depression for more than 24 hours while drinking. Both items were found to be rare in mild and moderate use disorder and highly prevalent (>60%) in severe AUDs. Having an independent anxiety or affective disorder and elevated scores on trait neuroticism were also significantly associated with the occurrence of both symptoms, as was alcohol “craving”, elevated treatment seeking, suicidal behaviors and drinking to relieve the symptoms (all adjusted p ’s <0.01, ORs range= 1.5–22).

Conclusions: Affective symptoms are common in severe AUDs, are associated with a history of independent affective/anxiety disorders, neuroticism, suicidal behaviors and may promote further heavy drinking.

Keywords

Alcohol use disorders; Anxiety disorders; Affective disorders; comorbidity; American Indians; Mexican Americans

INTRODUCTION

Alcohol use disorders (AUD) and major depressive disorders (MDD) have lifetime rates that are near 15% each, thus substantial co-morbidity of the disorders would be expected even by chance (see (1–3)). However, there is evidence to suggest that these disorders are causally linked (4). Heavy drinking and alcohol problems can lead to depressive syndromes that can at times mimic major depressive episodes (MDE), and are associated with substantial risk for suicide (5, 6). This syndrome was originally termed “secondary depression” and was later called a substance-induced MDE (see (1, 7, 8)). Substance-induced MDEs have been reported to be highly prevalent in alcoholics, perhaps explaining about half of the lifetime rates of MDEs overall in these populations (1, 8), but are said to be less common in epidemiological samples (9). A systematic review and meta-analysis of outcomes for independent and substance-induced MDEs concluded that few studies have fully examined the natural history and treatment response of substance-induced disorders (10, 11). Risk factors that predispose some individuals to develop substance-induced MDEs remain to be fully defined, however, some data suggest that a history of an independent mood disorder is a prominent risk (12).

Substance-induced mood disturbances can also affect drinking behaviors. Mood disturbance associated with withdrawal or “cutting down” on drinking, was commented on over half a century ago by Jellinek (13) who described the phenomena of “relief drinking” where the motive for drinking, was to alleviate distress or to avoid withdrawal. Laboratory based studies support this clinical description and provide evidence to suggest that depression severity, the tendency to drink in negative emotional situations, and the experience of alcohol “craving” can co-occur in some treatment seeking alcoholics (14, 15). A comprehensive theory of motives for drinking over the course of AUDs first for its positive

reinforcement value, and subsequently to relieve distress as anxiety and depressive syndromes emerge (drinking in response to “negative reinforcement”) has been posited, in various forms, by Solomon (16), Siegel (17), Baker (18), and Koob and colleagues (see (19–21)). Koob and colleagues have suggested that transient and perhaps subtler negative affective symptoms can emerge over the course of AUDs and that these symptoms may provide a motive for drinking to relieve distress. They have termed this phenomenon the “dark side” of alcohol addiction. While this is a powerful theoretical construct, the definition and quantification of the incidence of potential proxies of such “dark side” symptoms in large community samples of alcoholics have yet to be described.

In order to investigate “dark side” symptoms in large community based samples we used data from 3 studies, conducted by the authors, that included 2,568 individuals with AUDs of European American (EA), Mexican American (MA), and American Indian (AI) ancestry. The first formal aim of the study was to use this dataset to operationalize 2 simple phenotypes that encompass affective and anxiety symptoms associated with AUDs that can be obtained from a commonly used psychiatric interview (Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA)). Under the second aim, we test whether these 2 phenotypes were significantly associated with any demographic variables (age, gender, ethnicity, education, socio-economic status) first in the large EuroAmerican population that targeted participants with AUDs and then in the combined sample of the 2 minority populations that were more epidemiologically based. In the third aim we sought to track whether the two phenotypes occurred significantly more often in individuals who had reached a more severe clinical course/diagnosis of AUD or who were seeking treatment in the two populations. In the fourth aim, we determined whether the phenotypes were more likely to occur in participants who had comorbid conditions such as other Axis I psychiatric disorders, suicidal behaviors (in the minority populations where these data were available) and trait neuroticism. In the fifth aim we verified whether participants, with the two phenotypes, actually endorsed drinking to either relieve the affective symptoms or continued to drink despite knowing their drinking had caused the symptoms.

METHODS

Design:

Data from 3 retrospective cross-sectional studies were used to examine the existence and characteristics of negative affective “dark side” symptoms that are postulated to emerge over the clinical course of AUDs. Only participants with DSM-5 AUD (mild, moderate or severe) from the three larger populations were included in the analyses (n=2568). Analyses were first conducted in the large University of California San Francisco (UCSF) family study that specifically targeted participants with AUDs and no other Axis I diagnoses (n=1663), and then tested the aim in the combined AI and MA participant sample (n=905) that was more epidemiologically based. Additionally, the three samples were not combined due to differences in the SSAGA used in the UCSF as compared to the AI/MA study. The AI and MA samples were combined after power analyses revealed that small effect sizes could not be detected if the two samples were evaluated separately. These final samples were used to test study aims as described above.

Participants:

American Indians (AIs), were recruited from reservations, as described previously (22). AI participants were recruited across a wide age range (18–85 yrs.), and all eligible individuals in the population were targeted. The MA participants were recruited using a direct mailing list of Hispanic surnames in a local catchment area. The mailed invitation stated that potential participants must be of MA heritage, be between the ages of 18–30 years, be residing in the United States legally, and be able to read and write in English (see (23)). Based on the aims of these larger studies, participants were excluded if they were pregnant, nursing, or currently had a major medical disorder that precluded them traveling to the research site. Participants were asked to refrain from alcohol or recreational drug use for 24 hours prior to testing, and their breathalyzer blood alcohol levels had to be 0.00 g/dl to be included in the study. The protocols for both studies were approved by the Institutional Review Board of The Scripps Research Institute and for the AI study, the Indian Health organization for the tribes participating. Written informed consent was obtained from each participant after the study was fully explained.

The EA participants come from the UCSF family study. Participants were recruited through the use of semi-targeted direct mail, a web site, press releases, advertisements and from alumni of treatment centers, across the nation. Potential participants reporting significant drug use (defined as use of stimulants, cocaine, or opiates daily for more than 3 months or weekly for more than 6 months), current or past diagnosis of schizophrenia, bipolar disorder, or other psychiatric illness involving psychotic symptoms, a life-threatening illness, or an inability to speak and read English were excluded. Recruitment and assessment details have been previously published (24). Briefly, a remote data collection procedure was developed allowing for questionnaires to be returned by mail, and structured diagnostic interviews to be conducted by telephone. Potential participants first had the study explained and gave written informed consent.

Procedures:

Each AI and MA participant completed a face-to-face interview with the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), a validated instrument (25, 26) which collected information including demographics, psychiatric history, and symptoms of substance use disorders. The SSAGA generates DSM-IV diagnoses. In addition, the interview retrospectively asked about the occurrence of select alcohol-related life problems, including “craving” that we have demonstrated follow a defined temporal course indexing the severity of AUD (22, 27, 28) (see table 2, 3). For alcohol use disorders, DSM-IV diagnoses were translated to DSM-5 diagnoses by adding a craving criterion and subtracting the DSM-IV recurrent substance-related legal problem criterion from the 11 groups of DSM-IV dependence and abuse diagnostic symptoms and reassessing 12-month clustering for 2, 4, 6 criteria to generate DSM-5 mild, moderate, and severe disorder diagnoses, respectively. Lifetime diagnoses of other drug dependence (marijuana, stimulants, sedatives, hallucinogens, opioids, nicotine), antisocial personality disorder/conduct disorder (ASPD/CD), “any independent affective disorder” (major depressive disorder, dysthymia, bipolar I disorder), “any independent anxiety disorder” (social phobia, agoraphobia, panic disorder, obsessive compulsive disorder), and post-traumatic stress disorder (PTSD) in these

populations were defined by DSM-IV criteria. The SSAGA also contains information on suicidal behaviors including: ideation, plans, and attempts. Neuroticism was indexed by scores on the Maudsley personality inventory (29).

A modified version of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (27), was used for the UCSF study. Only the sections of the SSAGA relevant to substance misuse, demographics, and medical history were included. In the UCSF SSAGA, DSM-5 AUD mild, moderate, and severe diagnoses were made for totals of 2–3, 4–5, and 6 groups, respectively, and DSM-4 criteria for cannabis use disorder and nicotine use disorder were generated. All best final diagnoses for all studies were made by a research psychiatrist/addiction specialist (DAG). Neuroticism was indexed in a subsample of the UCSF population (n=476) using the short form of the Big Five Inventory (BFI) (30).

Two symptoms, that are a standard part of the SSAGA, were selected to be used as an index of substance-associated affective states or “dark-side symptoms”. The first was a measure of withdrawal that queried whether participants ever felt anxious or depressed when they stopped or cut down on drinking (yes/no). If the participant responded positively to that item, a second item was asked that queried if they had three or more times taken a drink to make those symptoms go away (e.g. “relief drinking”). The second “dark-side” measure queried whether participants’ drinking had ever caused them to feel depressed or uninterested in things for more than 24 hours and to the point that it interfered with their functioning (yes/no). If the participant responded positively to that item, a second item was asked that queried as to whether they had continued to drink after they knew that alcohol had caused that problem.

Statistical analysis

The first formal aim of the study was to operationalize 2 “dark side” phenotypes. To test reliability of the 2 items selected we used data from forty-five participants from the UCSF Family Study who had completed the SSAGA on two separate occasions and had valid responses for the two symptoms on both occasions. Tetrachoric correlations were run across time-points to estimate the test-retest reliability of each item, both of which were acceptable (affective symptoms when cutting down drinking - $r = 0.79$, experienced 24 hours of depression while drinking - $r = 0.92$). Power analyses were conducted in both population samples based on previous data (27, 28) and power was sufficient to test primary outcome variables (Power=0.8, $\alpha = 0.05$, OR=2.21, $n=786$ (small-medium effect size)). To test aims 2–5, first means and frequencies for demographic characteristics were compared for the two dark side symptoms in the UCSF and AI/MA samples using Chi Square for dichotomous variables and ANOVA for continuous variables to identify potential covariates (see table 1). The prevalence of the two affective “dark-side” symptoms in the two population samples (UCSF, AI +MA) were then calculated and multiple logistic regression used to determine associations between the two symptoms and: AUD severity level (see figure 1), 12 alcohol-related problems that index the clinical course (see table 2, 3) and the total number of those symptoms, select psychiatric disorders and symptoms (independent affective disorders, independent anxiety disorders, suicidal behaviors, antisocial personality disorder/conduct disorder, cannabis use disorder), in the AI/MA, and other substance use

disorders (cannabis dependence, nicotine dependence (UCSF only)), neuroticism in both populations, and “drinking to relieve” or “drinking despite having” affective symptoms associated with drinking, in both populations. Adjusted p-values, taking into consideration demographic covariates, were obtained from logistic regression and the significance level was determined by false discovery rate where relevant (31). Odds ratios and 95% confidence intervals were calculated from logistic regression adjusting for covariates in the analyses. Statistical analyses were conducted using SPSS v. 20.

RESULTS

Demographic characteristics for the two “dark side” symptoms in the UCSF and AI/MA sample are presented in Table 1.

Evaluation of the 2 affective “dark side” symptoms associated with drinking in the 1663 participants with AUDs in the UCSF sample revealed that 1021 (61%) endorsed the symptom of experiencing anxiety or depression after stopping or cutting down on drinking. Those who endorsed that symptom were more likely to be: female, not employed, to have an income below 20K, and to be unmarried (all $p < 0.01$). In the UCSF sample 926 (56%) participants endorsed having experienced 24 hours of depression while drinking that caused disability. Those participants who endorsed that item were more likely to be: unmarried and to have an income below 20K per year.

Evaluation of the 2 affective “dark side” symptoms associated with drinking in the 905 participants with AUDs in the combined AI/MA sample revealed that fewer overall participants endorsed the two symptoms as also seen in table 1. In the AI/MA sample (23%) endorsed the symptom of experiencing anxiety or depression after stopping or cutting down on drinking, and 216 (24%) participants endorsed having experienced 24 hours of depression while drinking that caused disability. Logistic regression revealed that when all demographic variables were entered that age and race were significant covariates, for the two symptoms in the AI/MA sample ($p < 0.01$).

Prevalence of “dark side” symptoms based on severity of alcohol use disorder: As seen in figure 1, both dark side symptoms were more like to occur in participants with severe use disorder in both populations. However, in the UCSF sample, of the 1381 participants with severe use disorder 72% endorsed feeling anxious or depressed when cutting down and 65% reported having experienced 24 hours of depression that caused disability while drinking. In contrast, in the AI/MA sample of the 372 participants with severe use disorder, fewer reported dark side symptoms, with 48% endorsing feeling anxious or depressed when cutting down and 49% reporting having experienced 24 hours of depression while drinking.

Associations between “dark side symptoms” and alcohol-related life problems indexing the clinical course of alcohol use disorders: Endorsing affective symptoms when drinking was significantly associated with several alcohol-related life problems that index the clinical course of alcohol use disorders as well as the total count of alcohol problems in both the UCSF and AI/MA sample. When all twelve symptoms were entered into a logistic regression controlling for significant covariates, endorsing affective symptoms when cutting

down and endorsing experiencing 24 hours of depression when drinking were found to be significantly associated with several individual alcohol problems, after controlling for false discovery rate, as well as the total number of alcohol problems endorsed ($p<0.001$) as seen in tables 2 and 3.

Associations between “dark side symptoms” and comorbid psychiatric diagnoses: In the UCSF sample, logistic regression that accounted for significant demographic variables demonstrated that having a severe AUD was a highly significant predictor of both symptoms (see table 4). Cannabis dependence and nicotine dependence were also tested for associations with the two affective symptoms. However, only severe AUD ($p<0.0001$) remained significant when entered into a logistic regression along with cannabis dependence, nicotine dependence and demographic variables, for the variable “affective symptoms when cutting down”. For the symptom “24 hours depressed while drinking” only severe AUD ($p<0.0001$) and cannabis dependence ($p<0.002$) were significant.

Consistent with the findings from the UCSF study, having a severe AUD was also found to be a highly significant predictor of both of the affective symptoms associated with drinking in the combined AI/MA population controlling for age and race (affective symptoms when cutting down: $p<0.0001$) (24 hours depressed while drinking: $p<0.0001$) as seen in Table 4. Endorsing affective symptoms when cutting down on drinking was also tested for associations with: anxiety disorders, antisocial personality disorder/conduct disorder, affective disorders and cannabis use disorder in the combined AI/MA sample. When all the disorders were added into the logistic regression together along with severe AUD only the presence of an affective disorder ($p=0.001$) and severe AUD ($p<0.0001$) remained significant. Endorsing experiencing 24 hours of depression when drinking was also tested for associations with the other psychiatric disorders together with severe AUD and only the presence of an affective disorder ($p<0.0001$), and an anxiety disorder ($P=0.002$) and severe AUD ($p<0.0001$) remained significant in the final model (see Table 4).

Associations between “dark side symptoms” and neuroticism: A small subset of the UCSF population also had data on neuroticism, as indexed by the Big 5 ($n=476$). Neuroticism scores were not associated with any of the demographic variables, however, the scores were found to be associated with the two affective symptoms: affective symptoms when cutting down ($p<0.003$, $OR=1.3$) and 24 hours depressed ($p<0.0001$, $OR=1.5$). This relation with neuroticism also remained significant when controlling for the presence of severe AUD.

Neuroticism, as indexed by the Maudsley, was also associated with the two affective symptoms in the AI/MA population (affective symptoms when cutting down ($p<0.0001$, $OR=1.1$) and 24 hours depressed ($p<0.0001$, $OR=1.1$) and both remained significant when entered into a logistic regression with severe AUD.

Associations between “dark side symptoms” and suicidal behaviors: Endorsing affective symptoms when drinking was also significantly associated with suicidal behaviors in the AI/MA population. Endorsing affective symptoms when cutting down on drinking was significantly associated with: suicidal plans ($p<0.001$, $OR=3.1$) and attempts ($p<0.0001$, $OR=3.25$). Endorsing experiencing 24 hours of depression when drinking was significantly

associated with all three suicidal behaviors: having suicidal ideation ($p<0.001$, $OR=2.0$) suicidal plans ($p<0.003$, $OR=2.7$) and attempts ($p<0.0001$, $OR=4.7$).

Dark side symptoms and motives for further drinking: Participants in the UCSF study were also queried as to whether they had, more than three times, drank to relieve affective symptoms associated with withdrawal (e.g. “relief drinking”). In the UCSF sample 68% ($n=693$) reported relief drinking, and it was found to be associated with having a severe AUD ($p<0.0001$, $OR=17.3$) and with the total count of alcohol problems ($p<0.001$, $OR=1.4$). Severe AUD ($p<0.0001$, $OR=8.3$), and the total count of alcohol problems ($p<0.001$, $OR=1.2$), were also both significantly associated with drinking despite knowing it caused depression for more than 24 hours.

Participants in the AI/MA study were also queried as to whether they had, more than three times, drank to relieve the symptoms when cutting down or stopping drinking (e.g. “relief drinking”). Forty-six percent ($n=114$) of those who reported affective symptoms when cutting down also reported relief drinking. Relief drinking was associated with the presence of a severe AUD ($p<0.000$, $OR=9.68$) and the total number of symptoms ($p<0.001$, $OR=1.2$), but no demographic variables or comorbidities. Drinking despite experiencing 24 hours of depression, was also associated with severe AUD ($p<0.0001$, $OR=8.16$), the total number of alcohol problems ($p<0.0001$, $OR=1.4$), but not with any of the other psychiatric disorders.

DISCUSSION

A number of studies have attempted to document a causal relationship between MDE's and AUDs. An examination of the wave 1 and wave 2 of the NESARC revealed that presence of a wave 1 MDE did not significantly increase the risk of substance use disorders at wave 2 (32). A longitudinal study in Canada found that MDE only increased the risk of alcohol dependence in men (33). Schuckit and colleagues (12) have stressed the importance of distinguishing between substance-induced MDE's and independent depressive episodes (IDEs) when interpreting longitudinal data on this potential bidirectional relationship. In their longitudinal study of 846 high-risk men they found that among probands who developed AUDs that 31% of the depressive episodes were substance-induced (12), and over a 3-decade follow-up period, that those men with IDE's had no increased rate of AUDs. Thus, available data suggest a complex relationship between alcohol and depressive syndromes with more evidence for AUDs increasing the risk of a depressive episode rather than vice-versa.

The prevalence of subtle, and perhaps more temporary, episodes of depressed mood that may emerge over the course of AUDs has been little explored in clinical studies. Our data demonstrate that simple queries concerning affective symptoms associated with drinking can be informative about several aspects of AUDs. We found few gender differences in the prevalence of the affective symptoms associated with drinking. We also found that affective symptoms associated with drinking emerge over the course of the evolving severity of AUDs, often late in the clinical course of the disorder (22, 27, 28). In the present study “Dark side” symptoms were significantly more common among those participants with

severe AUD and much less common in those with moderate or mild disorder. These data are consistent with the findings of Bulloch, (33) who stressed the importance of alcohol *dependence* and risk for MDE but who found no increased risk for excessive consumption or binge drinking and MDEs. In the present study, we additionally found that these affective symptoms are primarily related to *alcohol* use disorders as opposed to other co-morbid substance use disorders.

Schuckit and colleagues (34, 35), have described a series of alcohol-related life problems that define the clinical course of AUDs. In the present study, we found that some of these problems were also associated with the presence of the two affective symptoms. Experiencing “such a strong desire to drink that one could not think of anything else” was associated with “feeling anxious or depressed when stopping or cutting down” in both populations. Craving or strong desire to take a drug has long been considered one of the core features of addiction (36–38). It has been suggested that stressful situations and feelings of anxiety or depression may influence craving by triggering memories of the “relief” provided by alcohol (see (39, 40)). This is also a central premise of the phenomena of “stress-induced relapse” in alcoholism (41, 42). Our findings support the hypothesis that affective symptoms and craving co-exist in AUD, however, drinking to relieve these symptoms or despite the presence of affective symptoms, in the present study, was primarily explained by the overall severity of the disorder, and the total number of alcohol problems present.

The symptom of having experienced at least 24 hours of depression when drinking, was found to be associated with the symptoms of: “drinking having caused serious or repeated problems in a love relationship or marriage” and “feeling guilty about drinking” in both populations. The co-occurrence of these problems suggests the possibility that drinking may lead to a cascade of life problems that could promote depressive affect. The mechanism underlying this phenomenon has been suggested to involve alcohol-induced dysregulation of brain systems that are related to stress (43, 44). However, when drinking interferes with relationships it may cause psychosocial consequences that can also contribute to depressive affect like the loss of an important relationship.

While it is clear that “dark side” symptoms emerge in the context of severe alcohol use disorder, not all people with severe alcohol use disorder additionally report “dark side” symptoms. This suggests that perhaps certain trait variables may predispose some individuals to experience these symptoms more often than others. It has been suggested that affective symptoms and problems associated with drinking may be particularly prevalent in individuals with a predisposition toward independent affective disorders or affective traits (12, 45). Our study supports this premise as we found that a personal history of either an independent affective disorder or an independent anxiety disorder was associated with affective symptoms while drinking in the AI/MA. In addition, in both populations (AI/MA and UCSF) the trait personality characteristic of neuroticism was significantly associated with the presence of affective symptoms while drinking. While our study suggests an association between neuroticism and substance-induced affective symptoms it does not shed light on the directionality of this finding, and it is possible that drinking may enhance neurotic traits. Nevertheless taken together these findings suggest that certain individuals may be a higher risk for developing “dark side” symptoms, and that not all individuals with

severe AUDs may experience the symptoms. Our study also evaluated whether individuals who experienced dark side symptoms also reported drinking to relieve the symptom (in the case of depression/anxiety associated with withdrawal) or despite knowing that their AUD had caused the symptom (in the case of 24 hours of depression). In the UCSF sample 68% and in the AI/MA sample 46% of participants with “dark side” symptoms reported “relief drinking”. Thus having “dark side” symptoms may provide a motive for further drinking, however, it clearly does not do so in all persons experiencing the symptom.

We found that having affective symptoms associated with AUD was also significantly associated with treatment seeking in both study populations. These data may explain previous findings that have shown that substance-induced disorders are more commonly seen in treatment samples (46) than in epidemiological samples (9). “Dark side” symptoms were also found to be more common in the UCSF sample than the combined AI/MA sample which could also be due to the fact that the recruitment for the UCSF sample included treatment centers. Endorsing affective symptoms associated with drinking was also found to be significantly associated with suicidal behaviors in the AI/MA. Several studies provide data showing a strong association between alcohol use and suicide although a cohesive theory explaining this link is still emerging (see (47)). Our findings relate the emergence of substance-induced affective states over the course of AUD with increased risk for suicidal behaviors, a new finding that may in part help to explain their high co-morbidity.

In conclusion, the 2 affective symptoms associated with drinking, identified in the present study, were found to be highly prevalent (>50%) in severe AUDs. Having an independent anxiety or affective disorder and elevated scores on trait neuroticism were also significantly associated with the occurrence of the 2 symptoms, as was “craving”, elevated treatment seeking, and suicidal behaviors. The presence of the two affective symptoms was also significantly associated with endorsing “relief drinking” and/or drinking despite knowing that their AUD had caused the symptom. These findings support the overall theoretical construct described by Koob and colleagues (see (43)) that affective states referred to as “dark side” symptoms can emerge during the course of AUDs and motivate subsequent drinking. However, it appears that such symptoms do not appear in all individuals with severe AUDs and they do not motivate drinking in all persons experiencing the symptoms. This suggests that the appearance of “dark side” symptoms may not represent a distinct “stage of addiction” but rather a “subtype” of AUD that occurs in certain vulnerable individuals within the context of severe use disorder. This notion will certainly require further studies for confirmation or refutation.

Limitations and considerations:

The findings from this study should also be interpreted within the context of several limitations. The selected proxies of the “dark side” used in this study were limited to what was available in the assessment instruments used. The creation and use of more comprehensive queries and instruments of the “dark side” may document differences from the present study. While the major findings in the study were found in both of the current study populations, differences in recruitment techniques, demographics, and assessment instruments between the two samples limit the ability to detect potential ethnic/racial or

gender differences, and thus limit the generalizability of the findings. Since the SSAGA for the UCSF sample did not include ascertainment of psychiatric disorders or behaviors other than substance use, that sample was limited in its ability to detect the influence of major depressive episodes or other psychiatric conditions on affective symptoms associated with drinking in that population. It is important to note that this study collected retrospective, cross-sectional data on symptoms and disorders. The occurrence of “dark side” symptoms, as described by Koob and colleagues (20,21), are envisioned to unfold over a *longitudinal* course associated with perhaps years of drinking. Thus, the present findings would be greatly strengthened by confirmation in a prospective study.

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Distribution of the severity of alcohol use disorder in participants with and without “dark side” symptoms in the UCSF and AI/MA populations

In each graph the number of participants who endorsed the two “dark side” symptoms (dark bars) are compared to those who did not endorse having experienced the symptom (shaded bars) as a function of alcohol use disorder severity (mild, moderate, or severe AUD) is presented. Increasing severity of AUD coincides with significantly increased endorsement of “dark side” symptoms in both UCSF and American Indian/Mexican American populations.

However, significantly more participants in the UCSF sample had a severe AUD and those participants also endorsed more “dark side” symptoms.

Table 1. Demographics for “dark side” symptoms in the UCSF, American Indian/Mexican American study samples

Demographic Variable	UCSF Sample (n=1663)		American Indian/Mexican American Sample (n=905)	
	n (%)		n (%)	
	ANX/DEPR when cutting down or stopped		ANX/DEPR when cutting down or stopped	
	DEPR 24hrs while drinking		DEPR 24hrs while drinking	
Gender ¹				
Male	712 (43.0)	381 (53.5)	413(58.0)	423 (46.7)
Female	945 (57.0)	545 (57.7)	608 (64.3)	482 (53.3)
Married				
Yes	799 (48.1)	410 (51.3)	458 (57.3)	137 (15.2)
No	863 (51.9)	518 (60.0)	564 (65.4)	767 (84.8)
Employed				
Yes	1,092 (71.0)	604 (55.3)	646 (59.2)	404 (45.5)
No	445 (29.0)	254 (57.1)	294 (66.1)	484 (54.5)
Income \$20,000/yr				
Yes	1,248 (76.7)	675 (54.1)	743 (59.5)	527 (61.3)
No	380 (23.3)	236 (62.1)	256 (67.4)	333 (38.7)
Age (yrs) ²	46.8 (0.3)	46.6 (0.4)	46.8 (0.4)	28.9 (0.4)
Years of education ²	14.3 (0.07)	14.3 (0.1)	14.4 (0.1)	12.2 (0.06)
				11.9 (0.1)
				11.7 (0.1)

¹ Six participants declined to state gender.

² Mean and standard error presented; mean ± (SE)

Table 2.

Associations between alcohol problems and the “dark side” symptom of “feeling anxious or depressed when stopped or cut down drinking”

Alcohol Problem Variable	UCSF ¹			American Indian/Mexican American ²		
	Yes No n	p-value	OR(CI)	Yes No n	p-value	OR(CI)
Binging for 2 days straight	804 682	0.006 *	1.502(1.21,1.79)	467 434	NS	1.053(0.58,1.52)
Strong Desire	839 647	<0.001 *	1.893(1.61,2.21)	230 671	<0.001 *	2.561(2.15,2.98)
Drinking/recovering left no time for other activities	954 532	<0.001 *	1.722(1.42,2.03)	347 554	NS	1.575(1.12,2.03)
Drinking became so regular you would not change	611 875	NS	1.401(1.10,1.70)	229 672	0.01	1.817(1.36,2.28)
Arguments about drinking	1095 391	NS	0.895(0.59,1.20)	653 248	NS	1.486(0.94,2.03)
Hidden alcohol	787 699	0.001 *	1.638(1.35,1.92)	265 636	NS	1.277(0.86,1.70)
Given up activities to drink	927 559	0.01	1.478(1.17,1.78)	250 651	NS	1.719(1.27,2.16)
Drinking interfered with work, home, school	997 489	NS	1.244(0.93,1.56)	321 580	NS	1.242(0.81,1.68)
Drinking interfered with relationship	1003 483	NS	1.396(1.09,1.70)	287 614	0.005 *	1.816(1.40,2.23)
Feeling guilty	1261 225	0.004 *	1.752(1.37,2.13)	409 492	NS	1.155(0.75,1.56)
Blackouts	1177 309	0.001 *	1.743(1.41,2.07)	634 267	NS	1.008(0.51,1.51)
Seeking treatment	977 509	<0.001 *	2.316(2.03,2.60)	193 708	<0.001 *	2.474(2.05,2.89)
Total (x ± SE)	9.1 ±0.1 5.3 ±0.1	<0.001 *	1.551(1.48,1.63)	7.9 ±0.2 3.8 ±0.1	<0.001 *	1.546(1.45,1.65)

Items run in a logistic regression with significant demographic covariates:

¹ gender, employed, married and income,

² age and race.

* Significant corrected for FDR.

Table 3.

Association between alcohol problems and the “dark side” symptom of “Drinking caused you to feel depressed for 24 hours and to the point it interfered with functioning”

Alcohol Problem Variable	UCSF ¹			American Indian/Mexican American ²		
	Yes No			Yes No		
	<u>n</u>	<u>p-value</u>	<u>OR(CI)</u>	<u>n</u>	<u>p-value</u>	<u>OR(CI)</u>
Binging for 2 days straight	875 753	NS	1.333(1.07,1.60)	467 434	NS	1.422(0.96,1.89)
Strong Desire	910 718	<0.001 *	1.829(1.56,2.10)	230 671	NS	1.615(1.19,2.05)
Drinking/recovering left no time for other activities	1030 598	0.005 *	1.504(1.22,1.79)	347 554	NS	1.106(0.65,1.56)
Regular drinking, not change	670 958	0.01	1.412(1.14,1.68)	229 672	NS	1.506(1.04,1.98)
Arguments about drinking	1205 423	NS	1.197(0.91,1.48)	653 248	NS	1.60(1.06,2.14)
Hidden alcohol	865 763	NS	1.223(0.96,1.49)	265 636	NS	1.397(0.98,1.82)
Given up activities	1004 624	0.01	1.443(1.16,1.73)	250 651	0.005 *	1.869(1.43,2.31)
Drinking interfered with work, home, school	1086 542	<0.001 *	1.85(1.57,2.13)	321 580	NS	1.682(1.25,2.11)
Drinking interfered with relationship	1094 534	<0.001 *	1.757(1.48,2.04)	287 614	0.003 *	1.884(1.48,2.29)
Feeling guilty	1368 260	0.008 *	1.621(1.26,1.98)	409 492	<0.001 *	2.852(2.45,3.25)
Blackouts	1281 347	0.004 *	1.58(1.27,1.89)	634 267	NS	0.786(0.29,1.28)
Seeking treatment	1066 562	<0.001 *	1.883(1.62,2.15)	193 708	<0.001 *	2.402(1.98,2.82)
Total (means ± SE)	9.3 ±0.1 5.7 ±0.1	<0.001 *	1.534(1.47,1.60)	7.8 ±0.2 3.8 ±0.1	<0.001 *	1.578(1.48,1.69)

Items run in a logistic regression with significant demographic covariates:

¹ married and income,

² age and race.

* Significant corrected for FDR.

Table 4.

Associations between Axis I psychiatric disorders and the “dark side” symptoms.

UCSF (n=1663)									
Disorder	Feeling anxious or depressed when cutting down ¹			Depressed for 24hrs or more while drinking ²					
	No Dx (Y N)	Dx (Y N)	p-value	OR(CI)	No Dx (Y N)	Dx (Y N)	p-value	OR(CI)	
Mild AUD	1020 546	2 95			926 640	2 95			
Moderate AUD	997 481	25 160	0.01	6.9(1.6,30.2)	906 572	22 163	.01	6.8(1.6,29.6)	
Severe AUD	27 255	995 386	<0.001	20.2(13.1,31.3)	24 258	904 477	<0.001	18.6(11.9,29.0)	
Nicotine Dependence	350 310	672 331	ns		309 351	619 384	.01	1.4(1.1,1.7)	
Cannabis Dependence	800 550	222 91	ns		713 637	215 98	0.001	1.6(1.2,2.2)	
American Indian/Mexican American (n=905)									
Disorder	Feeling anxious or depressed when cutting down ³			Depressed for 24hrs or more while drinking ³					
	No Dx (Y N)	Dx (Y N)	p-value	OR(CI)	No Dx (Y N)	Dx (Y N)	p-value	OR(CI)	
Mild AUD	204 373	7 321			203 374	13 315			
Moderate AUD	186 514	25 180	<0.001	6.0(2.5,14.3)	195 505	21 184	0.007	2.7(1.3,5.5)	
Severe AUD	32 501	179 193	<0.001	13.1(8.5,20.2)	34 499	182 190	<0.001	13.8(8.9,21.5)	
Cannabis Dependence	124 493	87 201	ns		115 502	101 187	ns		
Any Anxiety disorder	145 548	66 146	ns		137 556	79 133	0.002	2.0(1.3,3.0)	
Any Affective disorder	118 481	93 213	0.001	2.0(1.4,3.0)	107 492	109 197	<0.001	2.8(1.9,4.2)	
ASPD/CD	147 578	64 116	ns		152 573	64 116	ns		

Items run in a logistic regression loaded with significant demographic covariates:

¹ gender, employed, married and income,² married and income,³ age and race. AUD=Alcohol Use Disorder, ASPD/CD=Antisocial Personality Disorder/Conduct Disorder.