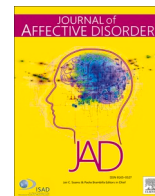




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Research paper

Patterns of demoralization and anhedonia during early substance use disorder treatment and associations with treatment attrition

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ABSTRACT

Background: Although depressive symptoms represent a promising therapeutic target to promote recovery from substance use disorders (SUD), heterogeneity in their diagnostic presentation often hinders the ability to effectively tailor treatment. We sought to identify subgroups of individuals varying in depressive symptom phenotypes (i.e., demoralization, anhedonia), and examined whether these subgroups were associated with patient demographics, psychosocial health, and treatment attrition.

Methods: Patients ($N = 10,103$, 69.2 % male) were drawn from a dataset of individuals who presented for admission to SUD treatment in the US. Participants reported on their demoralization and anhedonia approximately weekly for the first month of treatment, and on their demographics, psychosocial health, and primary substance at intake. Longitudinal latent profile analysis examined patterns of demoralization and anhedonia with treatment attrition as a distal outcome.

Results: Four subgroups of individuals emerged: (1) *High demoralization and anhedonia*, (2) *Remitting demoralization and anhedonia*, (3) *High demoralization, low anhedonia*, and (4) *Low demoralization and anhedonia*. Relative to the *Low demoralization and anhedonia* subgroup, all the other profiles were more likely to discontinue treatment. Numerous between-profile differences were observed with regard to demographics, psychosocial health, and primary substance.

Limitations: The racial and ethnic background of the sample was skewed towards White individuals; future research is needed to determine the generalizability of our findings to minoritized racial and ethnic groups.

Conclusions: We identified four clinical profiles that varied in the joint course of demoralization and anhedonia. Findings suggest specific subgroups might benefit from additional interventions and treatments that address their unique mental health needs during SUD recovery.

Depressive symptoms are prevalent among individuals in treatment for substance use disorders (SUDs) (Hunt et al., 2020; Moustafa et al., 2020), particularly during early SUD treatment (Sanchez et al., 2015). Higher depressive symptoms at SUD treatment intake and throughout the first month of treatment have been associated with earlier discharge (Gundel et al., 2017) including those who leave against medical advice (AMA) (Ellis et al., 2022). Although depressive symptoms may be one potential therapeutic target to promote treatment participation and reduce attrition, the heterogeneous nature of depressive symptoms and major depressive disorder (MDD) often pose an obstacle for developing clinically meaningful screenings and treatments (Fried, 2017). Indeed,

based on the DSM-5 criteria, there are approximately 230 combinations of symptoms that could lead to an MDD diagnosis, and it is possible that individuals who meet diagnostic criteria for MDD may have few to no symptoms in common (Ballard et al., 2018). Thus, it has been recently argued that an MDD diagnosis offers limited clinical utility and that a summary score of disparate symptoms may result in the loss of critical information (Fried, 2017; Fried et al., 2022). This may partially explain why MDD has been inconsistently related to SUD treatment outcomes as different symptom presentations may confer differential risk for SUD recovery (Ghabrash et al., 2020). Thus, targeting specific depressive symptoms may have greater potential in promoting the development of

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effective interventions given the clinical diversity in the diagnostic presentation of MDD (Kelly et al., 2022).

Anhedonia is commonly experienced among individuals with depressive symptoms and may be an important predictor of SUD treatment retention. Anhedonia refers to a reduced ability to experience pleasure, decreased responsiveness to natural rewards (e.g., food, positive social interactions), and reduced motivation and drive, all of which are thought to reflect deficits in neural reward processing (Borsini et al., 2020; Cooper et al., 2018; Hofflich et al., 2019; Wang et al., 2021). Approximately 40 % of individuals that experience anhedonia meet diagnostic criteria for MDD (Pelizza and Ferrari, 2009), and there is evidence that anhedonia is more common in individuals with SUD than controls (Dorard et al., 2008; Garfield et al., 2014; Stevens et al., 2007) and is associated with poorer SUD treatment outcomes (Huhn et al., 2019; Nguyen et al., 2020). Demoralization is a multi-faceted, complex psychological phenomenon that is also frequently reported among patients with SUDs (Tossani and Fava, 2013). Several researchers have conceptualized demoralization as existential distress; a loss of perceived agency; feelings of incompetence, despair, and isolation; and an inability to cope with stressors and meet expectations (Frank, 1985; Clarke et al., 2003). More recently, De Figueiredo (1993) suggest that the unique feature of demoralization is subjective incompetence that results in subsequent impairments in decision making. Both theoretical and empirical work have indicated that demoralization is a construct that is distinct from psychiatric disorders (Clarke et al., 2003; De Figueiredo, 1993).

Despite the potential clinical relevance of demoralization among individuals in SUD treatment, demoralization remains a relatively understudied construct among individuals in SUD treatment and has largely been examined in oncology and palliative care settings (Belvederi Murri et al., 2020; Tang et al., 2015). However, there are a number of reasons why demoralization may be particularly relevant to the experience of individuals in SUD treatment. Many patients in SUD treatment—especially early on in treatment—may find it difficult to control drug cravings and substance use (Dillon et al., 2020), which may lead to a lack of perceived agency and powerlessness, characteristic features of demoralization. Moreover, individuals seeking SUD treatment may have experienced negative consequences (e.g., hospitalization, legal problems, criminal justice system involvement (Moore et al., 2020; Tsai and Gu, 2019; Wu et al., 2018) as a result of their use, which may create additional barriers to fulfilling goals or life responsibilities, resulting in feelings of demoralization. Last, common to the experience of many individuals in SUD treatment is societal stigma (Crapanzano et al., 2019), which may become internalized and contribute to isolation, a core feature of demoralization. Further supporting the relevance of demoralization to individuals with SUDs is evidence that individuals with SUDs reported higher demoralization relative to the general population (De Weert et al., 2017). There is also evidence that individuals with opioid use disorder endorsed higher levels of demoralization than individuals diagnosed with cancer (De Jong et al., 2008). In addition, patients with SUDs who report demoralization have an almost 6-fold increase in the odds of developing a mood disorder (Tossani and Fava, 2013). Other work has shown that patients who dropped out of methadone maintenance treatment endorsed higher levels of demoralization at treatment intake relative to those who completed treatment (Chang et al., 2022). Taken together, these findings indicate that demoralization may be an important, novel, and clinically relevant phenotype that plays a role in SUD recovery.

However, less is known about patterns of anhedonia and demoralization symptoms during early SUD recovery, and correlates and outcomes associated with this joint course. Most research evaluating associations of anhedonia and demoralization with SUD treatment outcomes has used variable-centered approaches (e.g., correlations, structural equation modeling) (Laursen and Hoff, 2006). While variable-centered approaches are useful for describing associations among variables in a given sample, person-centered methods (e.g., longitudinal

latent profile analysis; LLPA) can enable the identification of homogeneous subgroups of individuals varying in anhedonia and demoralization symptoms over time. Although anhedonia and demoralization are distinct phenomena that can occur independently of each other (Clarke et al., 2000), it is possible that there may be overlap in the occurrence of these two states. Indeed, we previously found that patients who experienced clinically significant anhedonia reported marginally greater levels of demoralization, and that there were overlapping deficits in prefrontal cortex response to natural rewards that were associated with both anhedonia and demoralization (Huhn et al., 2021).

The identification of unique subgroups of individuals that vary in the intensity and temporal patterns of anhedonia and demoralization during early SUD treatment may lead to targeted interventions and greater precision of treatment approaches aimed at improving treatment completion. This is relevant, as attrition during substance use disorder (SUD) treatment is a common concern, with empirical studies and meta-analysis showing that between 30 %–70 % of individuals fail to successfully complete treatment (Allen and Olson, 2015; Lappan et al., 2020; Sinha, 2011). Importantly, studies have shown that treatment dropout often occurs early in treatment (i.e., the majority discontinue before the tenth session of outpatient treatment) (Şimşek et al., 2018) underscoring the importance of identifying factors associated with treatment retention during this period.

In the current study, we sought to address a number of gaps in the literature. First, leveraging person-centered techniques (i.e., LLPA), we aimed to identify clinical profiles of patients varying in anhedonia and demoralization over the course of the first month of SUD treatment. The identification of subgroups who vary in the severity of anhedonia and demoralization allows for a more comprehensive examination of the breadth of patient experiences during early SUD treatment. Second, we sought to identify whether participant demographics (e.g., gender), primary substance use that motivated treatment, and psychosocial variables (e.g., insomnia severity, stress) at intake could be used to predict heterogeneity in anhedonia and demoralization course. Third, we aimed to determine whether joint patterns of anhedonia and demoralization symptoms during early SUD recovery predicted treatment discontinuation.

1. Methods

1.1. Participants and procedure

Patients ($N = 10,103$) were drawn from a dataset of individuals who presented for admission to one of 73 SUD treatment facilities in the United States in 2021. 93.6 % of individuals initiated treatment in an inpatient/residential treatment center. Data were collected by a third-party treatment outcomes provider (Trac9.com). Across SUD treatment sites, patients self-reported on their symptoms and other indices of mental health through an online platform, which tracks patients' clinical symptoms and recovery. The measures used are standardized by Trac9 and delivered via a portal to patients in treatment, thus allowing for harmonized data collection across treatment centers. The study team received de-identified data via a data transfer agreement. The protocol was acknowledged by the Johns Hopkins School of Medicine Institutional Review Board (IRB00263214).

Individuals completed questionnaires at their treatment intake and measures during treatment (administered approximately weekly, though centers were able to determine when to assess patients). Demographic and substance use characteristics were assessed at intake. All other measures were given during the in-treatment surveys (described below).

1.2. Measures

1.2.1. Descriptive information assessed at treatment intake

1.2.1.1. Demographic and substance use characteristics. Participants reported their age, gender (dummy coded with female as the reference group), race, ethnicity, and employment status at treatment intake. Individuals were also asked to identify their primary substance leading into treatment. These categories were recoded into 1) Alcohol, 2) Cannabis, 3) Opioids or heroin, 4) Stimulants, including cocaine, methamphetamine, and other stimulants, and 5) Benzodiazepines. Alcohol was used as the reference group for the LLPA analysis.

1.2.2. Validated assessments: repeated-measures during treatment

Treatment locations chose when surveys were administered. On average, assessments were administered approximately weekly. Prior to running LLPA analyses, responses were binned by week (week 1 = 7 days \pm 3 days, week 2 = 14 days \pm 3 days, week 3 = 21 days \pm 3 days, week 4 = 28 days \pm 3 days). If individuals completed more than one survey in a given time period, the first survey was used.

1.2.2.1. Demoralization. The Demoralization Scale II is a 16-item questionnaire wherein patients rate a series of statements (e.g., “My life seems to be pointless”, “I feel quite isolated or alone”) on a 3-point Likert scale (0 = Never, 1 = Sometimes, 2 = Often). Higher scores indicate higher demoralization. The measure has been shown to have good internal and external validity (Robinson et al., 2016). Reliability was excellent in this sample (α s ranged from 0.940 to 0.949 across weeks in treatment). Patients completed repeated assessments of this measure during treatment.

1.2.2.2. Anhedonia. The Snaith-Hamilton Measure Scale (SHAPS) is a 14-item measure of anhedonia. Participants rated a series of statements (e.g., “I would enjoy being with my family or close friends”, “I would enjoy reading a book, magazine or newspaper”) on a 4-point scale ranging from “Strongly agree” to “Strongly disagree”. In line with the original scoring, the responses of “strongly disagree” or “disagree” were coded as 0, and the responses of “agree” or “strongly agree” were coded as 1. Reliability was good in this sample (α s ranged from 0.882 to 0.940 across weeks in treatment). The measure has been shown to have good psychometric properties (Franken et al., 2007), and is widely used in addiction research (Garfield et al., 2014). As with the demoralization measure, patients completed weekly assessments of the SHAPS.

1.2.3. Covariates assessed during treatment

The following assessments were included in models as covariates; only the first instance of these assessments was used.

1.2.3.1. Insomnia severity. The Insomnia Severity Index (ISI) is a seven-item measure of clinically meaningful symptoms of insomnia. Items are rated on a 5-point scale. The ISI has been shown to have excellent psychometric properties, including among patients with SUDs (Huhn et al., 2022). Reliability was excellent in each week in treatment (α s ranged from 0.926 to 0.939).

1.2.3.2. Optimism. The revised Life Orientation Test Revised (Carver et al., 2010) includes ten items (four of which are filler items) that are answered on a 5-point Likert scale ranging from “Strongly disagree” to “Strongly agree.” Reliability was good in this sample (α s ranged from 0.862 to 0.904 across weeks in treatment).

1.2.3.3. Depression severity. The Center for the Epidemiological Studies of Depression (CES–D) scale is a 20-item measure of depression severity (Radloff, 1977). Items are rated on a 4-point scale ranging from “Rarely or None of the Time” to “Most or all of the time.” Reliability was

excellent in each week in treatment (α s ranged from 0.913 to 0.942).

1.2.3.4. Anxiety Symptoms. The Penn State Worry Questionnaire (PSWQ) is a 16-item measure of trait worry (Meyer et al., 1990). Items are rated on a 5-point scale, ranging from “Not at all typical of me” to “Very typical of me.” Reliability was excellent in each treatment week (α s ranged from 0.947 to 0.955 across weeks in treatment).

1.2.3.5. Stress. The Perceived Stress Scale (PSS) is a 10-item measure of perceived stress (Cohen et al., 1983). Items are rated on a 5-point scale ranging from “Never” to “Very often.” Reliability was good in this sample (α s ranged from 0.886 to 0.913 across weeks in treatment).

1.2.4. Treatment outcome

Each treatment center recorded the patient's ultimate treatment outcome. Response options included 1) Administrative discharge, 2) Discharge against staff advice, 3) Elopement not returned, 4) Standard Discharge, and 5) Transfer facility. Here, we dichotomized these responses into discharged prior to treatment completion (options 1–3), which was coded as 1, vs. other treatment outcomes (options 4–5), which was coded as 0.

1.3. Data analysis

First, descriptive statistics and chi-square tests were used to contextualize the sample. Next, using Mplus, a longitudinal latent profile analysis (LLPA) was used to examine patterns of demoralization and anhedonia symptoms during the first four weeks of treatment. To address missing data, full information maximum likelihood (FIML) was used, which is appropriate in cases where data is expected to be missing at random or missing completely at random. Models were compared based on standard fit indices, including log-likelihood, Akaike information criterion (AIC), Bayesian information criterion (BIC), sample-size adjusted BIC, entropy, the smallest class size, the Vuong-Lo-Mendell-Rubin Likelihood Ratio (VLMR) test, and the Lo-Mendell-Rubin Adjusted Likelihood Ratio (LRT) test. Models were first run without covariates to identify the best-fitting model. After model selection, covariates were added to the model to identify model stability and to examine correlates of class membership. Treatment outcome was included as a distal outcome using the Bolck, Croon, and Hageaars (2004) method, also known as the BCH approach (Asparouhov and Muthén, 2014). The BCH method is a three-step approach to LLPA analyses that uses measurement error of latent classes (BCH weights) in estimating an auxiliary model predicting a distal outcome. This approach avoids shifts in latent classes. Descriptive data analyses were conducted in SPSS Version 27 (Armonk, NY), and LLPAs were conducted in MPlus Version 8.6 (Los Angeles, CA).

2. Results

2.1. Sample characteristics

A total of 10,103 individuals were included in the analysis. Sample characteristics are shown in Table 1. Approximately two-thirds of the sample was male, and the average age was 39.13 years (SD = 12.50). Approximately half of the sample (49.3 %) reported alcohol as their primary substance. Substantial proportions of patients reported that their primary substance was opioids or heroin (26.1 %) or stimulants (18.5 %). Fewer people reported marijuana (3.1 %) or benzodiazepines (2.9 %) as a primary substance.

2.2. Characterization of patterns of demoralization and anhedonia in early SUD treatment

Model fit indices without covariates are shown in Table 2. A four-

Table 1
Demographic characteristics.

Variable	N(%) or M(SD)
Gender	
Male	6996 (69.2 %)
Female	3085 (30.5 %)
Other	22 (0.2 %)
Race	
White	8195 (81.1 %)
Black/African American	1055 (10.4 %)
Other	663 (6.6 %)
Native American	97 (1.0 %)
Asian	63 (0.6 %)
Native American/Pacific Islander	26 (0.3 %)
Unknown/Missing	4 (0.00 %)
Ethnicity	
Hispanic or Latino	767 (7.6 %)
Not Hispanic or Latino	9329 (92.3 %)
Unknown/Missing	7 (0.1 %)
Primary Substance	
Alcohol	4983 (49.3 %)
Marijuana	317 (3.1 %)
Opioids/Heroin	2632 (26.1 %)
Stimulants (Cocaine, methamphetamines, or other stimulants)	1874 (18.5 %)
Benzodiazepines	297 (2.9 %)
Age, M(SD)	39.13 (12.50)

class model was selected because: 1) the degree of drop-off in the AIC, BIC, and SSA-BIC leveled off slightly after 4 classes, and 2) entropy did not improve beyond 4 classes; however, the smallest class size dropped to <5 % of the full sample, which may indicate model overfitting. The first class we identified was labeled *High demoralization and anhedonia*

Table 2
Model fit indices without covariates.

	Log-Likelihood	AIC	BIC	SSA-BIC	Entropy	Smallest class	LMR	VLRT
2 cl	142,928.233	285,906.467	286,086.981	286,007.535	0.946	11.2 %	0.064	0.065
3 cl	139,270.107	278,608.213	278,853.713	278,745.666	0.809	8.9 %	0.036	0.037
4 cl	136,606.838	273,299.675	273,610.161	273,473.513	0.826	5.4 %	0.002	0.002
5 cl	135,035.054	270,174.109	270,549.579	270,384.331	0.829	3.6 %	0.005	0.005
6 cl	133,784.951	267,691.903	268,132.359	267,938.510	0.829	2.5 %	0.184	0.189

Note. AIC = Akaike information criterion, BIC = Bayesian information criterion, SSA-BIC = Sample size adjusted Bayesian information criterion, Adj. LRT = Lo-Mendell-Rubin Adjusted Likelihood-ratio test, VLRT = Vuong-Lo-Mendell-Rubin Likelihood Ratio Test. Bold font indicates the model solution that was selected.

(5.4 %), which was characterized by persistently high demoralization and anhedonia over the first month of treatment. The second class, coined *Remitting demoralization and anhedonia* (9.7 %), was characterized by steady declines in demoralization across the first month of treatment, and very high levels of anhedonia in week 1 with a steep decline in week 2 that persisted. Class 3 was named *High demoralization, low anhedonia* (25.1 %) and evidenced clinically significant high levels of demoralization over the first month of treatment, but very low levels of anhedonia. Class 4 was named *Low demoralization and anhedonia* and evidenced very low levels of both anhedonia and demoralization throughout treatment (59.9 %).

2.3. Correlates of profile membership

With the inclusion of covariates, class sizes and latent profile shapes remained stable (5.4–59.9 % without covariates, 5.7–54.9 % with covariates). The profile shapes (adjusted for covariates) are depicted in Fig. 1. Correlates of profile membership are presented in Table 3. Relative to the *Low demoralization and anhedonia* group, membership in the *High demoralization and anhedonia* group was predicted by male gender, younger age, lower optimism, and higher depression, anxiety, insomnia, and perceived stress. Relative to the *Low demoralization and anhedonia* group, membership in the *Remitting demoralization and anhedonia* group was predicted by male gender, reporting opioids or benzodiazepines as one's primary substance, and higher depression, anxiety, insomnia, and perceived stress. Relative to the *Low demoralization and anhedonia* group, membership in the *High demoralization and low anhedonia* group was predicted by reporting marijuana as one's primary substance, lower optimism, and higher depression, anxiety, insomnia,

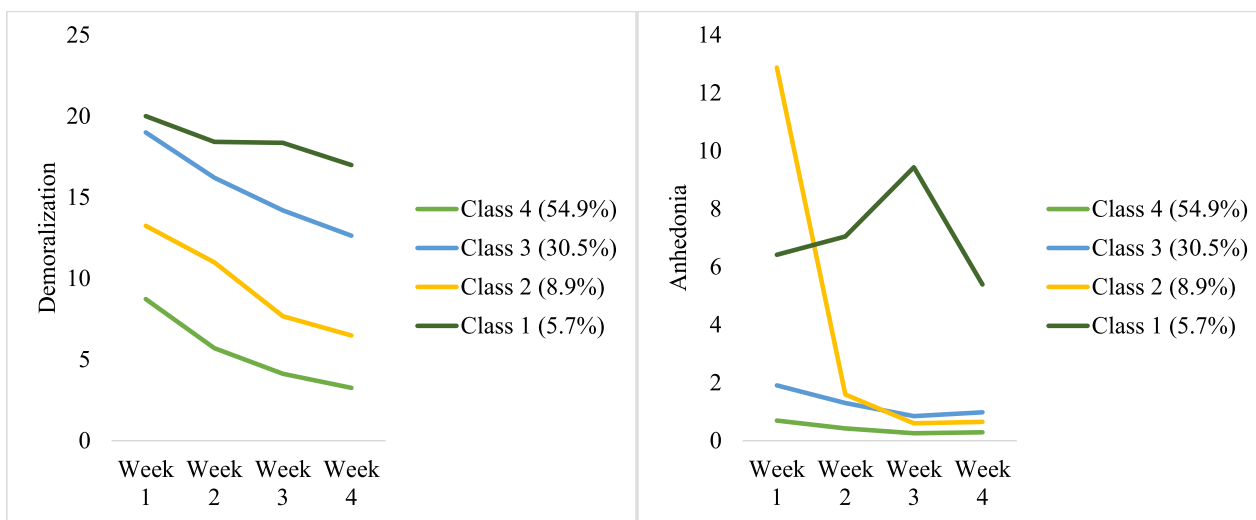


Fig. 1. Four-Class Model Means of Demoralization and Anhedonia During the First Month of Treatment
Class 1 = High demoralization and anhedonia, Class 2 = Remitting demoralization and anhedonia, Class 3 = High demoralization, low anhedonia, and Class 4 = Low demoralization and anhedonia.
Demoralization Range = 0–32, Anhedonia Range = 0–14.

Table 3
Correlates of class membership.

Variable	Class 1 vs. Class 4 (Ref.)	Class 2 vs. Class 4 (Ref.)	Class 3 vs. Class 4 (Ref.)
Female ^a	0.58 (0.46, 0.74)*	0.82 (0.68, 1.00)*	0.85 (0.73, 1.00)
Age	0.99 (0.98, 1.00)*	1.00 (0.99, 1.01)	1.00 (0.99, 1.00)
Primary Substance ^b			
Marijuana	1.76 (1.00, 3.09)	0.45 (0.17, 1.21)	1.86 (1.28, 2.72)*
Opioids	1.14 (0.87, 1.48)	3.23 (2.62, 3.99)*	1.13 (0.94, 1.34)
Stimulants	1.23 (0.93, 1.62)	0.84 (0.63, 1.13)	1.03 (0.85, 1.24)
Benzodiazepines	1.49 (0.86, 2.57)	1.83 (1.12, 2.99)*	0.96 (0.65, 1.44)
Depression Severity	1.08 (1.07, 1.10)*	1.07 (1.05, 1.08)*	1.07 (1.06, 1.08)*
Anxiety Symptoms	0.99 (0.98, 1.00)	1.02 (1.01, 1.03)*	1.01 (1.01, 1.02)*
Optimism	0.86 (0.84, 0.89)*	1.02 (1.00, 1.05)	0.88 (0.86, 0.89)*
Insomnia Severity	1.06 (1.05, 1.08)*	1.07 (1.05, 1.09)*	1.04 (1.03, 1.05)*
Perceived Stress	1.05 (1.02, 1.07)*	1.07 (1.05, 1.09)*	1.03 (1.02, 1.05)*

* $p < 0.05$.

^a Ref = Reported gender is male or other, 2. Ref = Primary substance is alcohol

^b Class 1 = High demoralization and anhedonia, Class 2 = Remitting demoralization and anhedonia, Class 3 = High demoralization, low anhedonia, and Class 4 = Low demoralization and anhedonia

and perceived stress. There were no other between-class differences observed.

2.4. Profile membership and probability of treatment discontinuation

Relative to the *Low demoralization and anhedonia profile*, all other classes were at a higher risk of discontinuing treatment (χ^2 values all >16.74 , $ps < 0.001$). In addition, relative to the *High demoralization, low anhedonia class*, individuals in the *Remitting demoralization and anhedonia profile* were more likely to discontinue treatment ($\chi^2 = 4.75$, $p = 0.029$). No other between-profile differences were observed with regard to treatment discontinuation.

3. Discussion

To our knowledge, this is the first longitudinal study to examine the joint course of demoralization and anhedonia among a SUD treatment seeking population. However, parallels can be made between our study and work by De Weert et al. (2017) that examined changes in demoralization among individuals in treatment for co-occurring SUDs and psychiatric conditions. Using variable-centered approaches, De Weert et al. (2017) found that patients exhibited significantly lower levels of demoralization at the end of the first month of treatment relative to treatment entry, which is in line with our findings showing that across the identified subgroups, there was a decline in reported demoralization. Declines in demoralization that were reported among a subgroup of participants in SUD treatment parallel findings from randomized controlled trials conducted among patients with psychiatric or chronic physical health or terminal conditions that observed reductions in demoralization (Fraguell-Hernando et al., 2020; Juliao et al., 2016; Sarizadeh et al., 2021). Numerous treatments that patients may receive during SUD treatment, such as individual counseling, group therapy, and/or pharmacological interventions may help decrease demoralization by increasing empowerment, competence, and human connectedness. Regardless, our findings highlight distinct subtypes of individuals that vary in the severity and stability of demoralization and anhedonia and suggest that specific subgroups might benefit from interventions that concurrently address SUDs and their unique mental health needs.

We also observed differences in risk for treatment dropout as a function of class membership. More specifically, individuals in the *High demoralization and anhedonia profile*, *Remitting demoralization and anhedonia* subgroup, and *High demoralization and low anhedonia* were more likely to discontinue treatment relative to the *Low demoralization*

and *anhedonia* subgroup. In addition, relative to the *High demoralization, low anhedonia* subgroup, individuals in the *Remitting demoralization and anhedonia* profile were at elevated risk for treatment dropout. High demoralization in the first week of treatment was common across classes that were at increased risk for treatment discontinuation, highlighting the importance of psychotherapeutic interventions that aim to instill purpose, restore morale, and encourage meaning-making in patients' lives during this period (Kiluk et al., 2019b; Strain et al., 2021). Moreover, behavioral or psychopharmacological treatments that focus on attenuating anhedonia symptoms (particularly among individuals in the *High demoralization and anhedonia* and *Remitting demoralization and anhedonia* profiles) may result in concomitant improvements in demoralization given shared neurobiological circuitry underpinning both clinical phenomena (Huhn et al., 2021); improving anhedonia symptoms might also promote treatment retention.

Between-profile differences were also observed in psychosocial health. For example, relative to the *Low demoralization and anhedonia* subgroup, all other subgroups evidenced elevated levels of depressive and anxiety symptoms, insomnia, and perceived stress. These results are consistent with variable-centered work indicating that anhedonia is related to co-occurring mental health conditions in persons with SUDs (Garfield et al., 2014; Xie et al., 2021), and with the overarching reward deficit/stress surfeit model of SUDs (Koob, 2013). Research among individuals with severe physical illness has shown moderate to high positive correlations between anhedonia and demoralization with trait anxiety and depression (Clarke et al., 2005). Our findings are also in line with research conducted in non-SUD populations linking greater perceived stress and sleep disturbances to alterations in incentive motivation and reward processing (markers of anhedonia) (Pizzagalli, 2014; Treadway et al., 2013; Wieman et al., 2021), and greater stress to higher demoralization (Harling et al., 2009). The fact that individuals with increased depressive and anxiety symptoms, insomnia, and perceived stress at intake were more likely to be in profiles characterized by higher levels of demoralization throughout treatment suggests that these individuals may benefit from adjunctive psychotherapies or pharmacological treatments that addresses these impairments, which may improve demoralization and anhedonia outcomes, as well as promote treatment adherence.

Demographic characteristics and primary substance that motivated SUD treatment were also linked to profile membership. In particular, relative to the *Remitting demoralization and anhedonia* subgroup, men and younger individuals were more likely to be in the *High demoralization and anhedonia* profile. Gender differences in profile membership may be partially explained by different patterns of substance use engagement prior to treatment and motivation for using substances. For example, men often engage in more polysubstance use compared to women (Hochheimer et al., 2020), which in turn, may lead to more difficult treatment induction and higher anhedonia (Barrot, 2015; Hu et al., 2004) and demoralization. In addition, acute abstinence may be associated with differential response to natural rewards among men and women given that men are more likely to use substances due to the positive reinforcing effects of substance use, whereas women are more likely to use substances to attenuate stress or negative affective states (Becker et al., 2012). Regarding the finding that younger individuals were more likely to be in the *High Demoralization and anhedonia* profile, older persons in SUD treatment (e.g., opioid use disorder treatment) are more likely to evidence medication adherence (Fishman et al., 2020), are less likely to have legal challenges and family problems at treatment intake (Brennan et al., 2003), and are more likely to be internally motivated to seek treatment (Bonfiglio et al., 2022; Goodman et al., 2011), which may buffer risk for feelings of demoralization and anhedonia. Future research examining factors that may be linked to gender and age differences in the demoralization and anhedonia profiles is warranted.

Relative to the *Low demoralization and anhedonia* profile, individuals in the *Remitting demoralization and anhedonia* subgroup were more likely

to report opioids or benzodiazepines as their primary substance. Individuals entering treatment for opioid or benzodiazepine use are likely to experience acute withdrawal, which has been associated with anhedonia (Barrot, 2015; Hu et al., 2004; Kiluk et al., 2019a). In SUD treatment settings, the administration of pharmacological interventions during the withdrawal period may improve mood and negative cognitive states, which may account for the decline in anhedonia and demoralization. In addition, compared to the *Low demoralization and anhedonia* profile, individuals in the *High demoralization, low anhedonia* subgroup were more likely to report marijuana as their primary substance. Of note, rates of residential treatment seeking among individuals who use cannabis are low, even when compared to treatment seeking rates among individuals who use other substances. Cannabis is the most widely used federally illegal substance; in 2020, an estimated 34.5 % of United States adults aged 18–25 and 16.3 % of United States adults older than 26 years used cannabis in the past year (National Survey on Drug Use and Health, 2020). However, only 3.1 % of individuals in the present sample were seeking treatment for primary cannabis use. Thus, it is possible that individuals entering treatment primarily for cannabis use may represent a high risk subgroup of individuals who use cannabis. Demoralization may be a risk factor for cannabis use progressing to severe cannabis use disorder, a possibility that should be explored in future studies. Alternatively, individuals engaged in cannabis use that is severe enough to warrant treatment may be experiencing consequences as a result of their use (e.g., legal challenges, difficulty sustaining employment), which may increase the likelihood of demoralization. It may be beneficial for future work to explore 1) the prevalence of cannabis-related consequences among individuals seeking treatment for cannabis use disorder, and 2) whether experiencing a greater number of cannabis-related consequences is associated with greater demoralization. Future studies should examine demoralization in these different groups.

Our study findings suggest that case management services and behavioral interventions that directly address demoralization and anhedonia may be beneficial. For example, in the classes characterized by high demoralization, case management services that directly help patients problem solve conditions perpetuating demoralization may help reduce demoralization symptoms. Examples include connecting patients record expungement services, childcare, employment opportunities, housing, and care for medical comorbidities. Further, among persons presenting with persistently high demoralization and/or high anhedonia, clinicians should encourage engagement in reinforcing activities, which may build feelings of esteem and competence (Martínez-Vispo et al., 2018; McHugh et al., 2010). Both anhedonia and demoralization can lead individuals to avoid tasks which require sustained effort, including tasks that had previously been reinforcing. However, avoiding previously enjoyable activities reduces opportunities to build esteem and mastery, and can worsen depressive symptoms. Thus, it is recommended that clinicians encourage engagement in such activities, while emphasizing and normalizing that doing so is unlikely to provide immediate reinforcement or relief. Rather, engaging in behaviors that are pleasurable and esteem-building build positive emotions over time, and provides an alternative activity to drug use. Clinicians can help provide structure and social reinforcement by helping patients set realistic and manageable small goals in each week of treatment. For patients who experience an abrupt decline in symptoms early in treatment (e.g., class 2) clinicians should work with patients to help reduce likelihood of symptom recurrence. Stabilized treatment with antidepressant medication and mindfulness-based interventions (e.g., mindfulness-based cognitive therapy, mindfulness-based relapse prevention) have both been shown to be efficacious in preventing recurrence of substance use disorders and depressive symptoms (Bowen et al., 2014; Nierenberg et al., 2003a, 2003b).

There are some limitations that should be acknowledged. First, the racial and ethnic background of the sample was skewed towards White/non-Hispanic individuals. While this is the largest racial/ethnic group of

persons with SUDs in the United States, understanding the unique experiences of minoritized groups is a top priority, and future research is needed to determine whether our findings generalize to minoritized racial and ethnic groups who are in SUD treatment. Second, although our research question was focused on determining the contributions of various psychosocial health variables (e.g., anxiety, stress, insomnia, optimism) at intake on the joint course of demoralization and anhedonia, it is likely that there are bi-directional relationships between indices of psychosocial health with demoralization and anhedonia over time. For example, experiencing demoralization and/or anhedonia may contribute to perceived stress or sleep disturbances, which in turn, may contribute to the maintenance or resurgence of demoralization and anhedonia. Therefore, future work should consider exploring the longitudinal, potential reciprocal associations between psychological, social, and mental health domains during early SUD recovery. Third, the data collection provider did not have access to formal SUD diagnoses, but rather asked participants entering SUD treatment about their primary substance of use. Fourth, data on patient withdrawal symptoms were not collected. It is possible that differences in withdrawal contribute to changes in reported demoralization and anhedonia. While the differences by primary substance suggest that factors like withdrawal or post-withdrawal effects may contribute to attrition, these factors are also the clinical reality of treatment and heterogeneity across different drug classes, an important area for prospective future research to investigate. Fifth, clinical diagnoses of psychiatric conditions were not available.

In conclusion, these findings suggest that although depressive symptoms and related sequelae are common among individuals seeking substance use treatment, clinical presentations of anhedonia and demoralization can vary cross individuals. These clinical presentations are differentially associated with treatment attrition and effectively tailoring treatment based on specific endorsement of symptoms may improve treatment outcomes. Given that anhedonia and demoralization are separate but related constructs, addressing both symptom trajectories may be important to improve SUD treatment outcomes.

CRediT authorship contribution statement

J. A. R. conceived of the study and wrote the introduction and discussion sections. J. D. E. conducted the analyses and wrote the methods and results section. M. H. and Y. Z. contributed to literature reviews. J. C. S. and A. S. H. provided feedback on the study conceptualization, and B. C. and A. S. Y. edited the manuscript.

Declaration of competing interest

The authors report no conflicts of interest.

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References

- Allen, R.S., Olson, B.D., 2015. Predicting attrition in the treatment of substance use disorders. *Int. J. Ment. Heal. Addict.* 14, 728–742.
- Asparouhov, T., Muthén, B., 2014. Auxiliary variables in mixture modeling: using the BCH method in Mplus to estimate a distal outcome model and an arbitrary secondary model. In: *Mplus Web Notes*, 21, pp. 1–22.
- Ballard, E.D., Yarrington, J.S., Farmer, C.A., Lener, M.S., Kadriu, B., Lally, N., Williams, D., Machado-Vieira, R., Nicu, M.J., Park, L., Zarate Jr., C.A., 2018. Parsing the heterogeneity of depression: an exploratory factor analysis across commonly used depression rating scales. *J. Affect. Disord.* 231, 51–57.
- Barrot, M., 2015. Ineffective VTA disinhibition in protracted opiate withdrawal. *Trends Neurosci.* 38, 672–673.
- Becker, J., Perry, A.N., Westenbroek, C., 2012. Sex differences in the neural mechanisms mediating addiction: a new synthesis and hypothesis. *Biol. Sex Differ.* 3, 14.
- Belvederi Murri, M., Caruso, R., Ounalli, H., Zerbinati, L., Berretti, E., Costa, S., Recla, E., Folesani, F., Kissane, D., Nanni, M.G., Grassi, L., 2020. The relationship between demoralization and depressive symptoms among patients from the general hospital: network and exploratory graph analysis. *J. Affect. Disord.* 276, 137–146.
- Bolck, A., Croon, M., Hagenars, J., 2004. Estimating latent structure models with categorical variables: One-step versus three-step estimators. *Pol. Anal.* 12 (1), 3–27.
- Bonfiglio, N.S., Renati, R., Agus, M., Penna, M.P., 2022. Development of the motivation to use substance questionnaire. *Drug Alcohol Depend.* 234, 109414.
- Borsini, A., Wallis, A.S.J., Zunszain, P., Pariante, C.M., Kempton, M.J., 2020. Characterizing anhedonia: a systematic review of neuroimaging across the subtypes of reward processing deficits in depression. *Cogn. Affect. Behav. Neurosci.* 20, 816–841.
- Bowen, S., Witkiewitz, K., Clifasefi, S.L., Grow, J., Chawla, N., Hsu, S.H., Carroll, H.A., Harrop, E., Collins, S.E., Lustyk, M.K., Larimer, M.E., 2014. Relative efficacy of mindfulness-based relapse prevention, standard relapse prevention, and treatment as usual for substance use disorders: a randomized clinical trial. *JAMA Psychiatry* 1, 71 (5), 547–556.
- Brennan, P.L., Nichol, A.C., Moos, R.H., 2003. Older and younger patients with substance use disorders: outpatient mental health service use and functioning over a 12-month interval. *Psychol. Addict. Behav.* 17, 42–48.
- Carver, C.S., Scheier, M.F., Segerstrom, S.C., 2010. Optimism. *Clin. Psychol. Rev.* 30, 879–889.
- Chang, T.G., Yen, T.T., Hsu, W.Y., Chang, S.M., 2022. Frontal lobe functions, demoralization, depression and craving as prognostic factors and positive outcomes of patients with heroin use disorder receiving 6 months of methadone maintenance treatment. *Int. J. Environ. Res. Public Health* 19.
- Clarke, D.M., Mackinnon, A.J., Smith, G.C., McKenzie, D.P., Herrman, H.E., 2000. Dimensions of psychopathology in the medically ill. A latent trait analysis. *Psychosomatics* 41, 418–425.
- Clarke, D.M., Smith, G.C., Dowe, D.L., McKenzie, D.P., 2003. An empirically derived taxonomy of common distress syndromes in the medically ill. *J. Psychosom. Res.* 54, 323–330.
- Clarke, D., Kissane, D.W., Trauer, T., Smith, G.C., 2005. Demoralization, anhedonia and grief in patients with severe physical illness. *World Psychiatry* 4, 96–105.
- Cohen, S., Kamarck, T., Mermelstein, R., 1983. A global measure of perceived stress. *J. Health Soc. Behav.* 24, 385–396.
- Cooper, J.A., Arulpragasam, A.R., Treadway, M.T., 2018. Anhedonia in depression: biological mechanisms and computational models. *Curr. Opin. Behav. Sci.* 22, 128–135.
- Crapanzano, K.A., Hammarlund, R., Ahmad, B., Hunsinger, N., Kullar, R., 2019. The association between perceived stigma and substance use disorder treatment outcomes: a review. *Subst. Abuse Rehabil.* 10, 1–12. <https://doi.org/10.2147/SAR.S183252>.
- De Figueiredo, J.M., 1993 Sep 1. Depression and demoralization: phenomenologic differences and research perspectives. *Psychiatry* 34 (5), 308–311.
- De Jong, C.A., Kissane, D.W., Geessink, R.J., Velden, D.V.D., 2008. Demoralization in opioid dependent patients: a comparative study with cancer patients and community subjects. *The Open Addict. J.* 1 (1).
- De Weert, G.H., Markus, W., Kissane, D.W., De Jong, C.A.J., 2017. Demoralization in patients with substance use and co-occurring psychiatric disorders. *J. Dual Diagn.* 13, 136–143.
- Dillon, K.S., P.J., Isehunwa, O.O., Sharma, M., 2020. Motivations for treatment engagement in a residential substance use disorder treatment program: a qualitative study. In: *Substance Abuse: Research and Treatment*, 1178221820940682.
- Dorard, G., Berthoz, S., Phan, O., Corcos, M., Bungener, C., 2008. Affect dysregulation in cannabis abusers: a study in adolescents and young adults. *Eur. Child Adolesc. Psychiatry* 17, 274–282.
- Ellis, J.D., Rabinowitz, J.A., Wells, J., Liu, F., Finan, P.H., Stein, M.D., Ii, D.G.A., Hobelmann, G.J., Huhn, A.S., 2022. Latent trajectories of anxiety and depressive symptoms among adults in early treatment for nonmedical opioid use. *J. Affect. Disord.* 299, 223–232.
- Fishman, M., Wenzel, K., Scodes, J., Pavlicova, M., Lee, J.D., Rotrosen, J., Nunes, E., 2020. Young adults have worse outcomes than older adults: secondary analysis of a medication trial for opioid use disorder. *J. Adolesc. Health* 67, 778–785.
- Fraguell-Hernando, C., Limonero, J.T., Gil, F., 2020. Psychological intervention in patients with advanced cancer at home through individual meaning-centered psychotherapy-palliative care: a pilot study. *Support Care Cancer* 28 (10), 4803–4811. <https://doi.org/10.1007/s00520-020-05322-2>.
- Frank, J.D., 1985. Further thoughts on the anti-demoralization hypothesis of psychotherapeutic effectiveness. *Integr. Psychiatry* 3, 17–26.
- Franken, I.H., Rassin, E., & Muris, P., 2007. The assessment of anhedonia in clinical and non-clinical populations: further validation of the Snaith–Hamilton Pleasure Scale (SHAPS). *J. Affect. Disord.* 99, 83–89.
- Fried, E.L., 2017. Moving forward: how depression heterogeneity hinders progress in treatment and research. *Expert. Rev. Neurother.* 17, 423–425.
- Fried, E.L., Flake, J.K., Robinaugh, D.J., 2022. Revisiting the theoretical and methodological foundations of depression measurement. *Nat. Rev. Psychol.* 1, 358–368.
- Garfield, J.B., Lubman, D.I., Yucel, M., 2014. Anhedonia in substance use disorders: a systematic review of its nature, course and clinical correlates. *Aust. N Z J. Psychiatry* 48, 36–51.
- Ghahash, M.F., Bahremand, A., Veilleux, M., Blais-Normandin, G., Chicoine, G., Sutra-Cole, C., Jutras-Aswad, D., 2020. Depression and outcomes of methadone and buprenorphine treatment among people with opioid use disorders: A literature review. *J. Dual Diagn.* 16 (2), 191–207.
- Goodman, I., Peterson-Badali, M., Henderson, J., 2011. Understanding motivation for substance use treatment: the role of social pressure during the transition to adulthood. *Addict. Behav.* 36, 660–668.
- Gundel, R., Allen Iii, N., Osborne, S., Shwayhat, S., 2017. Risk factors for early discharge from a residential addiction treatment program. *J. Addict. Res. Ther.* 08.
- Harling, M., Strehmel, P., Schablon, A., Nienhaus, A., 2009. Psychosocial stress, demoralization and the consumption of tobacco, alcohol and medical drugs by veterinarians. *J. Occup. Med. Toxicol.* 4, 4.
- Hochheimer, M., Sacco, P., Ware, O.D., 2020. Latent classes of lifetime drug use disorder in national epidemiological survey on alcohol and related conditions—III. *Addict. Behav.* 106, 106379.
- Hoflich, A., Michenthaler, P., Kasper, S., Lanzenberger, R., 2019. Circuit mechanisms of reward, anhedonia, and depression. *Int. J. Neuropsychopharmacol.* 22, 105–118.
- Hu, X.T., Basu, S., White, F.J., 2004. Repeated cocaine administration suppresses HVA-Ca²⁺ potentials and enhances activity of K⁺ channels in rat nucleus accumbens neurons. *J. Neurophysiol.* 92, 1597–1607.
- Huhn, A.S., Sweeney, M.M., Brooner, R.K., Kidorf, M.S., Tompkins, D.A., Ayaz, H., Dunn, K.E., 2019. Prefrontal cortex response to drug cues, craving, and current depressive symptoms are associated with treatment outcomes in methadone-maintained patients. *Neuropsychopharmacology* 44, 826–833.
- Huhn, A.S., Brooner, R.K., Sweeney, M.M., Antoine, D., Hammond, A.S., Ayaz, H., Dunn, K.E., 2021. The association of prefrontal cortex response during a natural reward cue-reactivity paradigm, anhedonia, and demoralization in persons maintained on methadone. *Addict. Behav.* 113, 106673.
- Huhn, A.S., Ellis, J.D., Dunn, K.E., Sholler, D.J., Tabaschek, P., Burns, R., Strain, E.C., 2022. Patient-reported sleep outcomes in randomized-controlled trials in persons with substance use disorders: a systematic review. *Drug Alcohol Depend.* 237, 109508.
- Hunt, G.E., Malhi, G.S., Lai, H.M.X., Cleary, M., 2020. Prevalence of comorbid substance use in major depressive disorder in community and clinical settings, 1990–2019: systematic review and meta-analysis. *J. Affect. Disord.* 266, 288–304.
- Juliao, M., Nunes, B., Barbosa, A., 2016. Prevalence and factors associated with demoralization syndrome in patients with advanced disease: results from a cross-sectional Portuguese study. *Palliat Support Care* 14 (5), 468–473.
- Kelly, C.A., Freeman, K.B., Schumacher, J.A., 2022. Treatment-resistant depression with anhedonia: integrating clinical and preclinical approaches to investigate distinct phenotypes. *Neurosci. Biobehav. Rev.* 136, 104578.
- Kiluk, B., Yip, S.W., DeVito, E.E., Carroll, K.M., Sofuoglu, M., 2019a. Anhedonia as a key clinical feature in the maintenance and treatment of opioid use disorder. *Clin. Psychol. Sci.* 7, 1190–1206.
- Kiluk, B.D., et al., 2019b. What defines a clinically meaningful outcome in the treatment of substance use disorders: reductions in direct consequences of drug use or improvement in overall functioning? *Addiction* 114, 9–15.
- Koob, G.F., 2013. Addiction is a reward deficit and stress surfeit disorder. *Front. Psychiatry* 4, 73.
- Lappan, S.N., Brown, A.W., Hendricks, P.S., 2020. Dropout rates of in-person psychosocial substance use disorder treatments: a systematic review and meta-analysis. *Addiction* 115, 201–217.
- Laursen, B., Hoff, E., 2006. Person-centered and variable-centered approaches to longitudinal data. *Merrill-Palmer Q.* 52, 377–389.
- Martínez-Vispo, C., Martínez, Ú., López-Durán, A., Fernandez del Rio, E., Becona, E., 2018. Effects of behavioural activation on substance use and depression: a systematic review. *Subst. Abuse Treat. Prev. Policy* 13 (1), 1–13.
- McHugh, R.K., Hearon, B.A., Otto, M.W., 2010. Cognitive behavioral therapy for substance use disorders. *Psychiatr. Clin.* 33 (3), 511–525.
- Meyer, T., Miller, M.L., Metzger, R.L., Borkovec, T.D., 1990. Development and validation of the penn state worry questionnaire. *Behav. Res. Ther.* 28, 487–495.
- Moore, K.E., Oberleitner, L., Pittman, B.P., Roberts, W., Verplaetse, T.L., Hacker, R.L., McKee, S.A., 2020. The prevalence of substance use disorders among community-based adults with legal problems in the U.S. *Addict. Res. Theory* 28 (2), 165–172. <https://doi.org/10.1080/16066359.2019.1613524>.
- Moustafa, A.A., Tindle, R., Cashel, S., Parkes, D., Mohamed, E., Abo Hamza, E., 2020. Bidirectional relationship between heroin addiction and depression: Behavioural and neural studies. In: *Current Psychology*.
- National Survey on Drug Use and Health. U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. Retrieved from. <https://www.samhsa.gov/data/report/2020-nsduh-annual-national-report>.
- Nguyen, L.C., Durazzo, T.C., Dwyer, C.L., Rauch, A.A., Humphreys, K., Williams, L.M., Padula, C.B., 2020. Predicting relapse after alcohol use disorder treatment in a high-risk cohort: the roles of anhedonia and smoking. *J. Psychiatr. Res.* 126, 1–7.

- Nierenberg, A.A., Petersen, T.J., Alpert, J.E., 2003 Jan 1. Prevention of relapse and recurrence in depression: the role of long-term pharmacotherapy and psychotherapy. *J. Clin. Psychiatry* 64 (15), 13–17.
- Nierenberg, A.A., Petersen, T.J., Alpert, J.E., 2003b. Prevention of relapse and recurrence in depression: the role of long-term pharmacotherapy and psychotherapy. *J. Clin. Psychiatry* 64 (15), 13–17.
- Pelizza, L., Ferrari, A., 2009. Anhedonia in schizophrenia and major depression: state or trait? *Ann. General Psychiatry* 8, 22.
- Pizzagalli, D.A., 2014. Depression, stress, and anhedonia: toward a synthesis and integrated model. *Annu. Rev. Clin. Psychol.* 10, 393–423.
- Radloff, L., 1977. The CES-D scale: a self-report depression scale for research in the general population. *Appl. Psychol. Meas.* 1 (385-301).
- Robinson, S., Kissane, D.W., Brooker, J., Michael, N., Fischer, J., Franco, M., Burney, S., 2016. Refinement and revalidation of the demoralization scale: the DS-II—internal validity. *Cancer* 122, 2251–2259.
- Sanchez, K., Walker, R., Campbell, A.N., Greer, T.L., Hu, M.C., Grannemann, B.D., Nunes, E.V., Trivedi, M.H., 2015. Depressive symptoms and associated clinical characteristics in outpatients seeking community-based treatment for alcohol and drug problems. *Subst. Abus.* 36, 297–303.
- Sarizadeh, M.S., Rahimian Boogar, I., Talepasand, S., Gharemanfard, F., 2021. Acceptance and commitment therapy for demoralization syndrome and cancer-related trauma: a randomized clinical trial study. *Int. J. Cancer Manag.* 14 (11) <https://doi.org/10.5812/ijcm.114637>.
- Şimşek, M., Dinç, M., Ögel, K., 2018. Determinants of the addiction treatment drop-out rates in an addiction counseling centre: a cross-sectional study. *Psychiatry Clin. Psychopharmacol.* 29, 446–454.
- Sinha, R., 2011. New findings on biological factors predicting addiction relapse vulnerability. *Curr. Psychiatry Rep.* 13, 398–405.
- Stevens, A., Peschk, I., Schwarz, J., 2007. Implicit learning, executive function and hedonic activity in chronic polydrug abusers, currently abstinent polydrug abusers and controls. *Addiction* 102, 937–946.
- Strain, E.C., Kampman, K.M., Weiss, R.D., 2021. Moving beyond medications that act at the mu receptor in the treatment of opioid use disorder. *JAMA Psychiatry* 78, 701–702.
- Tang, P.L., Wang, H.H., Chou, F.H., 2015. A systematic review and meta-analysis of demoralization and depression in patients with cancer. *Psychosomatics* 56, 634–643.
- Tossani, E., Fava, G.A., 2013. Psychosomatic approach to clinical practice. In: *Somatization and Psychosomatic Symptoms*, pp. 75–90.
- Treadway, M.T., Buckholtz, J.W., Zald, D.H., 2013. Perceived stress predicts altered reward and loss feedback processing in medial prefrontal cortex. *Front. Hum. Neurosci.* 7, 180.
- Tsai, J., Gu, X., 2019. Utilization of addiction treatment among U.S. adults with history of incarceration and substance use disorders. *Addict. Sci. Clin. Pract.* 14 (1), 9. <https://doi.org/10.1186/s13722-019-0138-4>.
- Wang, S., Leri, F., Rizvi, S.J., 2021. Anhedonia as a central factor in depression: neural mechanisms revealed from preclinical to clinical evidence. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 110, 110289.
- Wieman, S.T., Hall, K.A.A., MacDonald, H.Z., Gallagher, M.W., Suvak, M.K., Rando, A.A., Liverant, G.I., 2022. Relationships among sleep disturbance, reward system functioning, anhedonia, and depressive symptoms. *Behav. Therapy* 53 (1), 105–118.
- Wu, L.T., Zhu, H., Ghitza, U.E., 2018. Multicomorbidity of chronic diseases and substance use disorders and their association with hospitalization: results from electronic health records data. *Drug Alcohol Depend.* 192, 316–323. <https://doi.org/10.1016/j.drugalcdep.2018.08.013>.
- Xie, J., Fang, P., Zhang, Z., Luo, R., Dai, B., 2021. Behavioral inhibition/activation systems and depression among females with substance use disorder: the mediating role of intolerance of uncertainty and anhedonia. *Front. Psychiatry* 12, 644882.