A Comparison of Independent Depression and Substance-Induced Depression in Cannabis, Cocaine, and Opioid Dependent Treatment Seekers

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Abstract

Depressive symptoms often co-exist with substance use disorders (SUDs). The DSM-IV has identified two distinct categories for depression coexisting with SUDs – independent depression and substance-induced depression. While this distinction has important therapeutic and prognostic implications, it remains difficult to make in clinical practice; the differentiation is often guided by chronological and symptom severity criteria that patients may be unable to precisely provide. Furthermore, it is unclear whether the various substances commonly abused – cannabis, cocaine, and opioids – are equally associated with the two types of depression. Predictors, associations, and other markers may be helpful in guiding the diagnostic process. We therefore examined the differences between cannabis, cocaine, and opioid dependent individuals contending with independent depression and those contending with substance-induced depression in regards to several variables, hypothesizing that independent depression is more commonly found in females, and that it is associated with higher symptom severity and psychiatric comorbidity. Cocaine, cannabis, and/or opioid dependent, treatment-seeking individuals underwent a SCID after providing consent at our clinical research site; those with coexisting primary depression or substance-induced depression diagnoses were provided with further questionnaires and were entered into this analysis (n=242). Pair-wise comparisons were conducted between the groups classified as independent versus substance induced depression with 2 by 2 tables and chi-square tests for dichotomous independent variables, and t-tests for continuous variables. Binomial logistic regression was performed in order to ascertain which of the variables were significant predictors. Women were more likely than men to have independent depression (p<0.005). Cannabis dependence was highly associated with independent depression (p<0.001), while cocaine dependence was highly associated with substance-induced depression (p<0.05). Independent depression was associated with higher HAMD scores (16 vs. 10, p<0.005), and was more highly associated with the comorbid diagnosis of PTSD (p<0.05). Cannabis dependence (p<0.001) and female gender (p<0.05) were highly significant predictors of major depression specifically. Gender, cannabis dependence, psychiatric severity, and psychiatric comorbidity have variable, statistically significant associations with independent and substance-induced depression, and may be helpful in guiding the diagnostic process.

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Introduction

Substance use disorders (SUDs) and depressive symptoms often co-exist in clinical practice.[1] The Diagnosis and Statistical Manual for Psychiatric Illness, 4th ed., (DSM-IV-TR) recognizes two distinct presentations of coexisting depression – independent depression, and substance-induced depression. According to the DSM-IV-TR, independent depression emerges outside the context of drug use, cannot be entirely attributed to drug use by clinical judgment, and persists even when abstinence is maintained, while substance-induced depression, though warranting clinical attention, occurs only within the context of drug use and is expected to resolve with abstinence.[2]

These sub-classifications of co-occurring depression may be significant for a variety of reasons. According to expert opinion, co-occurring depression is best addressed immediately with anti-depressants or psychotherapy, while substance-induced depression is best managed by carefully observing its course and focusing care on the SUD primarily.[3] This strategy has been validated for alcohol but has yet to be investigated for other substances; two meta-analyses support the efficacy of antidepressant medication treatment among patients with co-occurring depression and alcohol dependence, the strongest effects demonstrated in studies where patients were required to be abstinent before depression was diagnosed.[4] Furthermore, the two types of co-occurring depression may be associated with different prognoses, both in respect to the depressive illness and the SUD, though this is an area of some controversy.[3,5-7] The pathology underlying each presentation may also be different, as are the phenomena – related to both the SUD and depression – that come to clinical attention in each case.[10]

Group differences between the two diagnostic categories have been investigated in some detail. Various research groups have examined the historical and phenomenological distinctions between independent and substance-induced depression co-occurring with alcohol dependence, with or without cocaine and opioid dependence.[5,6,8,9] Fewer analyses have examined differences in the purely opioid and cocaine dependent population,[11,12] while no studies have investigated this distinction in the cannabis dependent population. Most of these studies have found that female gender, higher severity of depressive illness and the presence of psychiatric comorbidity are consistently predictive of independent depression.[6,8,9,11] This is less clear, however, for cocaine, cannabis, and opiate dependent individuals.

We therefore compared treatment-seeking individuals with cannabis, cocaine, and opioid SUDs and lifetime independent or substance-induced depression in regards to demographic and clinical characteristics. As has been found in other studies, we hypothesized that patients with a history of substance-induced depression, as compared to those with a history of independent depression, would be more frequently male and less likely to be contending with psychiatric comorbidities. We also hypothesized that the severity of depressive symptoms would differ significantly between the two groups, with current substance-induced depression yielding a lower mean score on the Hamilton depression scale (HAMD) than does current independent depression. The temporal factors in delineating the two diagnoses – with substance use generally preceding the emergence of depressive symptoms in substance-induced depression – led us to further hypothesize that the age at which regular drug use began would be lower in the substance-induced depression group. Significant associations were further analyzed to determine which variables serve as significant predictors of diagnosis class.

Subjects and Methods

Subjects

Subjects were cocaine, cannabis, and/or opiate dependent individuals with co-existing depression seeking treatment at our university-based research clinic. They were recruited from the New York City metropolitan area by subway, television, and radio advertisements. Individuals were initially screened over the phone, and potential participants were asked to come in for further evaluation. During the initial evaluation, participants met with a psychologist who performed a structured clinical interview for DSM-IV-TR disorders (SCID) modified to delineate between primary and secondary depression with good interrater reliability.[15] They also filled out various questionnaires, discussed further below. Adults, aged 18-65, were eligible for this analysis if they met DSM-IV-TR criteria for dependence on opiates, cocaine, or cannabis, as well as a diagnosis of lifetime independent depression or substance-induced depression. Over the course of the 2 years that screening data were collected, from September 2007 to August 2009, there were 242 individuals who met criteria for inclusion into this analysis. Table 1 compares group characteristics based on depression. 176 individuals (72.7%) in our sample carried a diagnosis of lifetime independent depression [dysthymic disorder (DD) or MDD], while 66 individuals (27.3%) carried a diagnosis of lifetime substance-induced depression. 118 individuals (48.8%) had active independent depression, while 60 individuals (24.8%) had active substance-induced depression. For individuals with both diagnoses (n=13), the active diagnosis was decisive in determining group inclusion.

Procedures

Subjects underwent a modified SCID during their initial evaluation administered by a psychologist. DSMIVTR criteria were used to make all diagnoses. In addition to investigating for the usual criteria for depressive disorders (MDD, for example, involving at least five symptoms with one core symptom, and occurring most of the time for at least two weeks), the modified SCID differentiates between primary and secondary depression, a temporal distinction guided by ascertaining first onset of regular substance use, first onset of mood disorder, and the presence or absence of mood disorder during prolonged periods of abstinence. Referring to this distinction, our group went on to diagnose independent disorders as depressive episodes that generally emerge outside the context of regular drug use, and that persist during periods of abstinence. For depressive episodes that emerge during regular drug use but for which no period of abstinence occurred, we assessed the severity of the depressive symptoms, and if clinical judgment suggested that the symptoms were too severe to be accounted for by substance-induced depression alone (persistent suicidality, severe debility, emergence of depressive symptoms not accounted for by drug use), then a diagnosis of independent depression was made. Furthermore, a pre-existing diagnosis of an independent depressive episode did not lead us to presuppose that subsequent episodes were manifestations of the same independent disorder; each episode was evaluated separately, particularly if it occurs in the context of drug use. The SCID was also used to diagnose other psychiatric conditions and to ascertain the number of stressors.

Data analysis

SPSS® was used to carry out all analyses. Pair-wise comparisons were conducted between the groups classified as independent versus substance induced depression with 2 by 2 tables and chi-square tests for dichotomous independent variables, and t-tests for continuous variables. Dichotomous independent variables found to be significantly different by chi-square analysis were included in a unidirectional step-wise multivariate logistic regression to determine which were significant predictors of a major depression diagnosis specifically.

Results

Table 1 compares group characteristics based on depression. There were no significant differences between the two groups in regard to age, ethnicity, educational level, relationship status, number of stressors, age at which regular substance use began, diagnosis of an alcohol use disorder, or employment. As expected, significant differences were found by chi-square analysis between the two categories in regards to gender, HAMD scores, and presence of psychiatric comorbidity, post-tramautic stress disorder (PTSD) specifically.

Men in our sample were found to be more likely than women to have substance-induced depression (28% vs. 18.4%; p <0.05). Women were found to be more likely than men to have been diagnosed at some point in their lives with independent depression (72.4% vs. 53.5%; p<0.005). Most of the difference was accounted for by variability in the incidence of major depression disorder (MDD), with both men and women having similar rates of dysthymia. As shown in Table 2, female gender was a significant predictor of the diagnosis of MDD; OR: 1.940, 95% CI (1.08, 2.09), p < 0.05.

HAMD scores were found to be significantly higher in the independent depression group [which includes subjects diagnosed with MDD or DD] as compared to the substance-induced depression group (16.2 vs. 10.4, p = 0.002). HAMD scores did not differ significantly between groups based on gender. Also, HAMD scores did not differ significantly between groups based on type of drug dependence.

The incidence of PTSD was higher in the group with primary depression group as compared to the substance-induced depression group (12.5% vs. 5%; p <0.05). Rates for substance-induced anxiety disorders (SIADs) were comparable between the two groups. Other comorbid psychiatric conditions, such as other anxiety disorders, were not common enough in our sample to be included in the analysis. As with gender, most of the variability in regards to PTSD was accounted for by different representations of MDD. When a multivariate logistic regression was carried out in regards to MDD, however, PTSD was not a significant predictor for that diagnosis.

There was no difference between depression categories in regards to the age at which regular drug use began. When subjects within the independent depression group were regrouped according to the onset of their mood disorder and then compared with one another, it was found that the early-onset group (onset of symptoms before age 21) was associated with a significantly earlier age at which drug use began than was the late-onset group (onset of symptoms after age 21) (17.9 years of age vs. 23 years of age; p =0.001).

Cocaine dependent individuals had the highest incidence of substance-induced depression (p<0.001). Conversely, the cannabis dependent group had the highest incidence of independent depression (p<0.001), with most of the effect accounted for, as with gender and PTSD, by differences in the frequencies of MDD among the three groups. Of independent variables, cannabis dependence was found to be a statistically significant predictor of MDD (p<0.001).

Discussion

In this analysis, we compared substance-dependent individuals with a history of depression and investigated for statistically significant differences between those with independent depression and those with substance-induced depression. As expected, we found that independent depression was significantly associated with female gender, a higher HAMD score, and a higher incidence of psychiatric comorbidity, PTSD specifically. We also found that cannabis dependence is highly associated with independent depression. Given that most

group differences were accounted for by variable representations of MDD, a multivariate logic regression was carried out in regards to that diagnosis. Female gender and cannabis dependence emerged as significant predictors of MDD, but the diagnosis of PTSD did not.

The gender differences observed in our sample have been observed in other studies comparing substance-induced depression and MDD in the alcohol dependent or abusing population, as well as in epidemiology studies of MDD.[8,9,13] Our analysis extends this finding to the cocaine, cannabis, and opiate dependent treatment-seeking population, and further identifies female gender as a significant predictor of MDD diagnosis in this sample. This difference may be attributed to the well-documented likelihood for females to be diagnosed with independent depression disorders, and in our sample, MDD specifically.

Similar analyses conducted with the alcohol disordered population have observed that being married, Caucasian ethnicity, and older age are predictive of independent depression.[8,9] Perhaps because of our small, cross-sectional sample, we did not find these differences.

As expected, HAMD scores were significantly higher in the independent depression group. Other studies have found a difference in severity between the two types of depression in mainly the alcohol disordered population. Independent depression has been found to be more highly associated with suicidality, with a greater number of symptoms, and with a greater number of lifetime depressive episodes.[8,9,11] This is the first analysis, however, to find that the two groups differ in HAMD ratings, with the substance-induced group yielding a lower score. A similar analysis performed with opiate dependent Iranian individuals with primary or substance-induced depression found that the substance-induced depression group had significantly *higher* HAMD scores than did the independent depression group,[12] contrary to the DSM-IV-TR conceptualization of substance-induced depression as a mood disorder of lower severity than is independent disorder.

Another marker of illness severity may be the presence of comorbid psychiatric disorders. As expected, PTSD was more highly associated with the independent depression group in our sample. PTSD is an anxiety disorder that responds to anti-depressant medications, suggesting shared pathophysiological mechanisms with depression.[14] The co-occurrence of PTSD and depression in the SUD population has been previously observed in a longitudinal study conducted on alcoholics with depression, with the comorbid diagnosis of PTSD at baseline associated with independent depression and/or depressed mood on follow up.[6] Unlike gender, however, PTSD was not a significant predictor of MDD.

While we failed to find a difference between the two groups in regards to age at which regular drug use began, we found that earlier onset of regular drug use is more highly associated with early onset (before age 18) mood disorders than with late onset mood disorders. This suggests that even when a substance use disorder is not directly inducing a depressive disorder, there is a temporal relationship between the two. The nature of this relationship – whether it is due to the depressive disorder driving the drug use, or to an underlying pathological state common to the two disorders – requires further investigation.

An interesting finding was the high association between cannabis dependence and independent depression. While the literature on this subject is limited, there is general agreement that cocaine dependence and opiate dependence can lead to substance-induced depression;[11] there is far less literature regarding the association of marijuana dependence with depressive disorders. A substantial literature, however, has been devoted to the endocannabinoid system and depression.[16] The endocannabinoid system has been implicated in mood regulation, and endocannabinoid CB1 receptor agonists have shown antidepressant-like properties in animal studies.[16] It is therefore possible that cannabis may be used by some in order to ameliorate their mood symptoms, in line with the self-

medication hypothesis. Interestingly, of the five subjects who met criteria for both cocaine dependence and cannabis dependence, four carried the diagnosis of an independent disorder.

Other studies have made similar observations, finding that different drugs of abuse had variable associations with the two categories of coexisting depression. In a recent analysis, an alcohol use disorder alone is most highly associated with an independent depression; the co-occurrence of an opiate and/or cocaine use disorder, in addition to an alcohol use disorder, is more strongly predictive of substance-induced depression.[9] There may be other substances, moreover, that serve as predictors. The number of cigarettes smoked, for example, has been found to vary between the two groups in a recent analysis, with those diagnosed with independent depression smoking a greater number of cigarettes (>10) a day than those with substance-induced depression.[9]

Even though a majority of cannabis dependant individuals were diagnosed with independent depression, a substantial number was also diagnosed with cannabis-induced depression, a disorder that is not explicitly mentioned in the DSM-IV-TR. This finding suggests that the relationship between depression and cannabis is complex, and that while cannabis may be used by some to self-manage their depressive symptoms, it may be exacerbating or precipitating depressive symptoms in others. Further, it gives additional support to the hypothesis that cannabis-induced depression is a valid clinical entity.

There are a few important limitations to this study that should be noted. The assessments used in this analysis did not include other descriptors that may have been significant, such as ratings of life-time suicidality, personality disorder diagnosis, family history of depressive illness, and number of depressive episodes. An elucidation of drug use patterns may also have been helpful in determining significant differences between the two depression groups. The sample was relatively small and cross-sectional, and this may have limited our ability to observe differences.

Another limitation is the diagnostic challenge that depressive symptoms co-existing with SUDs present. While the distinction our group drew between independent depression and substance-induced depression was predicated on DSMIV criteria, and while uniform diagnostic procedures were adhered to by screening psychologists, there remains a risk of variability in making the distinction, particularly as the clinician's subjective judgment may be necessary in distinguishing between the two disorders in less clear-cut cases. This may have contributed, in part, to the differences observed among the different substance groups. The lack of an assessment of inter-rater reliability for the independent and substance-induced distinction constitutes a related limitation.

Despite these limitations, this analysis is the first to compare independent depression and substance-induced depression in the cocaine, opiate, and cannabis dependent population. The observed differences were similar, in general, to those found by previous researchers, and were primarily accounted for, in our sample, by differences between MDD and substance-induced depression. The association we observed between independent depression and cannabis dependence is interesting and deserves further attention. Further analyses of these and other associations – in larger epidemiology studies utilizing a greater number of variables and descriptors, and using more rigorous diagnostic instruments with good interrater reliability – will assist in determining their generalizability and elucidating their clinical relevance, as well as clarifying if there are other significant differences between the two diagnostic categories. Future studies can also consider investigating the effect of depression category on SUD prognosis, illness course, and response to treatment.

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Table 1

A Comparison of Group Characteristics Between Coexisting Independent Depression and Substance-Induced Depression in Actively Substance-Dependent Individuals

	Independent Depression, Current or in remission	Substance-induced Depression, (n=176) Current (n=66)
Age, in years (SD)	38.5 (10.2)	36.4 (9.1)
Ethnicity, %		
African American	31.5	39.9
Caucasian	39.4	32.7
Hispanic	18.9	18.8
Asian	6.1	5.5
Other	4	3.1
Relationship Status, % In a relationship	59	54
Education, in years (SD)	13.9 (2.1)	12.7 (2.3)
Employment, % Employed	61	60
Female, % [*]	40.3 (n=71)	24.2 (n=16)
Coc Dependence, % [**]	24.4 (n=43)	48.4 (n=32)
Opioid Dependence, %	22.2 (n=35)	33.3 (n=22)
THC Dependence, % [**]	55.7 (n=98)	19.7 (n=12)
HAMD (SD) [***], [c]	16.22 (5.8)	10.43 (3.9)
Age of initiating regular drug use, in years (SD)	19.2 (6.2)	19.3 (6.6)
Number of stressors (SD)	1.1 (1.1)	1.23 (1)
Current Alc abuse, %	5.2 (n=9)	4.5 (n=3)
Current Alc dep, %	15.3 (n=27)	16.7 (n=11)
Past AUD [1],%	40.3 (n=71)	33.3 (n=22)
PTSD [2], % [*]	13.1 (n=23)	4.5 (n=3)
SIAD [3], %	5.1 (n=9)	9.1 (n=6)

[*] $p < 0.05$;

[**] $p < 0.001$;

[***] $p < 0.005$

*(a)*Values in the table are means (standard deviations) or percent (number)

*(b)*Test statistics are chi-square for dichotomous independent variables, and t-tests for continuous variables

*(c)*HAMD scores were obtained from subjects with active diagnoses

*(1)*Alcohol Use Disorder,

*(2)*Post-traumatic Stress Disorder,

*(3)*Substance-induced Anxiety Disorder

Table 2

Effect of Variables on Major Depressive Disorder Diagnosis, Odds Ratios (95% Confidence Interval)

Variables	Major Depression
THC Dependence	3.123 (1.78, 5.47) [*]
Gender (Female)	1.940 (1.08, 2.09) [**]
Coc Dependence	0.598 (0.30, 1.18)
PTSD	1.176 (0.45, 3.07)

[*] $p < 0.001$,

[**] $p < 0.05$