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Gender Differences in Internalizing Symptoms and Suicide Risk Among Men and Women Seeking Treatment for Cannabis Use Disorder from Late Adolescence to Middle Adulthood

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ABSTRACT

Cannabis continues to rise in popularity as the perception of its harmfulness decreases and evidence of its deleterious developmental effect increases. While internalizing distress and suicide risk have been linked with cannabis use problems [*DSM-5* cannabis use disorder (CUD); *DSM-IV* cannabis abuse and dependence] it remains unclear how this association varies over the course of development in treatment-seeking men and women. The current study utilized the National Drug Abuse Treatment Clinical Trials Network (NIDA CTN) to conduct a cross-sectional comparison of internalizing distress and suicide risk among men ($n = 437$) and women ($n = 163$) spanning ages 18–50 who met *DSM-5* criteria for CUD. Interactions between gender and developmental stage (i.e., late adolescence, early adulthood, and middle adulthood) were observed for suicide risk and anxiety but not depression problems. Specifically, women seeking CUD treatment in late adolescence and middle adulthood exhibited significantly higher rates of anxiety and suicide risk compared to men seeking treatment during the same developmental stages. Internalizing distress and suicide risk did not differ between treatment-seeking men and women in the early adult stage. Overall, results suggest that the structure of risk for CUD may differ in men and women across the lifespan and that women presenting for CUD treatment during late adolescence and middle adulthood may uniquely benefit from intervention designed to address these elevations in anxiety and suicide risk.

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1. Introduction

Already the most commonly used illicit drug worldwide (United Nations Office on Drugs and Crime, 2010), cannabis continues to gain popularity (SAMHSA, 2013) as the perception of its harmfulness decreases (Compton, Grant, Colliver, Glantz, & Stinson, 2004; Johnston, O'Malley, Bachman, & Schulenberg 2013). Concurrently however, evidence of the deleterious developmental effect of cannabis use is prominent (Budney & Moore, 2002; Hall & Degenhardt, 2009; Volkow, Baler, Compton, & Weiss, 2014). Prolonged and compulsive cannabis use increases vulnerability to cannabis use disorder [*DSM-5* cannabis use disorder (CUD); *DSM-IV* cannabis abuse and dependence] and its associated psychosocial impairments. In particular, internalizing symptoms like anxiety, depression, and suicide risk have been routinely linked with CUD yet the relationship between these factors and CUD severity remains unclear (Buckner et al., 2008; Degenhardt, Hall, & Lynskey, 2003; Grotenhermen, 2003; King, Iacono, & McGue, 2004; McQueeny et al., 2011; Van Dam, Bedi, & Earleywine, 2012). Prior research suggests that psychosocial problems—like internalizing symptoms—that co-occur with alcohol use disorders likely vary by gender and development (Foster, Hicks, Iacono, & McGue, 2014; Hicks, Iacono, & McGue, 2010) but these variations have yet to be characterized for CUD. Directly testing gender differences in the relative severity of anxiety, depression, and suicide risk among those with CUD from late adolescence through middle adulthood will be an important step in further clarifying their role in CUD severity and effectively tailoring clinical intervention.

As men constitute 75% of the population of cannabis users (SAMHSA, 2013), women have historically been underrepresented in investigations of cannabis use problems. Consequently, understanding of gender-specific risks and consequences that co-occur with CUD during the transition from adolescence through middle adulthood is limited. Prior research on use of both alcohol and cannabis in men and women has detected that women paradoxically exhibit more severe psychosocial risks and consequences for use compared to men (Foster, Hicks, Iacono, & McGue, 2015; Khan et al., 2013) even though they develop problems with both substances less frequently (e.g., 5.4% of adult women compared to 11.8% of adult men meet criteria for lifetime cannabis dependence; Stinson, Ruan, Pickering, & Grant, 2006). Specifically, women exhibit higher sensitivity to the acute effects of

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cannabis (e.g., Cooper & Haney, 2014), greater vulnerability to the deleterious neurodevelopmental effects of protracted cannabis use (e.g., McQueeny et al., 2011), and experience larger reductions in quality of life and greater social stigma surrounding cannabis use (e.g., Lev-Ran et al., 2012). With these significant deterrents averting cannabis use in women, higher levels of premorbid risk exposure are likely more prevalent among the small proportion of women who develop CUD. Subsequently, higher rates of both psychosocial risks and consequences are likely to coincide with CUD in women compared to men.

Though internalizing distress is more prevalent among women, this distress appears to have a gender specific relationship with alcohol and cannabis use problems (Foster et al., 2014; Foster et al., 2015; Khan et al., 2013). For example, women with CUD exhibit higher rates of major depression than men with CUD (Khan et al., 2013). Additionally, anxiety has been shown to temporally predict the emergence of cannabis use problems later in development (Buckner et al., 2008). While research comparing these effects in men and women is limited, internalizing symptoms are a stronger predictor for alcohol and other illicit drug use problems in women compared to men (Foster et al., 2015), suggesting that the same pattern is likely present for CUD. Furthermore, both depression and anxiety have also been identified as important predictors of CUD relapse for women compared to men (Flórez-Salamanca et al., 2013). While these studies establish the importance of expanding knowledge regarding gender differences in cannabis use, gender differences in the relative importance of anxiety, depression, and suicide risk in CUD severity has not been thoroughly explored.

The time when CUD is present during development may also be a key determinant of the severity of psychosocial problems in men and women. Cannabis problems generally emerge in adolescence (Swift, Coffey, Carlin, Degenhardt, & Patton, 2008; Volkow et al., 2014; Wagner & Anthony, 2002), escalate through early adulthood (Jager, Schulenberg, O'Malley, & Bachman, 2013; Tucker, Ellickson, Orlando, Martino, & Klein, 2005), and stabilize through middle and later adulthood (Chen & Kandel, 1995; Coffey, Lynskey, Wolfe, & Patton, 2000; Kandel & Davies, 1992). Cannabis problems emergent during atypical periods of risk (i.e., adolescence or middle adulthood) may be associated with more severe psychosocial problems compared to those that emerge during a more common period (i.e., early adulthood) (Chen & Kandel, 1995; Hicks et al., 2010; Schuster, O'Malley, Bachman, Johnston, & Schulenberg, 2001; Tucker et al., 2005).

While developmental typologies are understudied in CUD samples, those for other substance use problems are well documented. For instance, men with alcohol use problems emergent during early adulthood (i.e., when risk for substance use problems escalates and role transition begins) often exhibit a developmentally-limited course wherein few preceding risks and long-term consequences are evident (Babor et al., 1992; Hicks et al., 2010; Leggio, Kenna, Fenton, Bonenfant, & Swift, 2009). Similar developmental patterns are not evident in women as risks and consequences associated with alcohol use problems appear uniformly severe (Foster et al., 2014). To determine if similar typologies of risk are present for CUD, studies are needed to estimate the severity of co-occurring psychosocial problems like internalizing symptoms across these key periods of transition in the lifespan (i.e., adolescent, early adulthood, and middle adulthood) when social roles and CUD prevalence typically shift.

When taken together, previous literature suggests that internalizing distress is likely elevated for CUD in women compared to men and that this relationship likely varies by development. While multiple studies have estimated the base rates of internalizing disorders co-occurring with CUD, few studies have directly compared the degree of severity of these symptoms in a clinical sample of men and women with CUD. Prior study has typically focused on a single developmental period (i.e., either adolescence or adulthood), precluding estimation of how shifting role responsibilities across developmental periods (e.g., increasing independence from primary caregivers, career initiation, marital relationships, parenthood) moderate the psychosocial problems linked with CUD. Defining these risk factors and their prominence across key demographic variables of developmental stage will provide additional insight into treatment barriers that require additional attention.

To address these limitations, the current study estimated anxiety, depression, and suicide risk among men and women who meet *DSM-5* criteria for CUD during the transition from late adolescence to middle adulthood (i.e., age 18-50). A cross-sectional developmental framework was used to organize our analyses around direct gender comparisons at periods of development that coincide with shifts in CUD prevalence (i.e., late adolescent onset, young adult escalation, and middle adult persistence) and key social role transitions (i.e., increasing personal independence in late adolescence, increasing responsibility in young adulthood, and stabilization through middle adulthood). Severity of internalizing distress among those with CUD is hypothesized to vary by both gender and developmental stage such that women with CUD would have higher levels of internalizing distress relative to men with CUD and that these differences would increase in parallel with developmental shifts in CUD risk.

2. Materials and methods

2.1. Clinical sample and setting

Participants ($N = 600$) were treatment-seeking men and women between 18 and 50 years of age screened for their eligibility for a 12-week clinical efficacy trial of *N*-acetylcysteine (NAC) for cannabis cessation (see McClure et al., 2014 for details of the larger trial). The current sample was composed of all participants who met *DSM-5* criteria for CUD in the previous 30 days, irrespective of their eligibility for the larger trial. Participating clinical sites were identified through the National Drug Abuse Treatment Clinical Trials Network (NIDA CTN) that spans clinical settings across the United States. To increase the representativeness of the CUD sample, efforts were made to recruit the same proportions of minorities present in the communities of each site. Using their age, participants were further divided into developmental groups that reflect distinct periods of CUD prevalence rates and social role responsibilities: late adolescence (i.e., age 18–22; when personal independence increases and CUD onset occurs in both genders), early adulthood [i.e., age 23–40; when CUD prevalence escalates and significant role transitions involving career, marital relationship(s), and parenthood occur], and middle adulthood (i.e., age 41 and over; when CUD prevalence and social responsibilities typically stabilize) (Chen & Jacobson, 2012; Englund et al., 2013; Perkonigg et al., 2008).

2.2. Assessment

Following brief pre-screening to ascertain the probability of CUD via phone or in-person, participants provided IRB-approved written informed consent prior to entering a baseline assessment phase. Over 1-week, trained study personnel conducted a battery of diagnostic, medical and psychosocial assessments to attain initial information about each participant before being randomized into the clinical trial.

2.2.1. CUD diagnosis and substance use variables

During the baseline assessment, trained staff administered the *DSM-IV* checklist to diagnose lifetime cannabis abuse and dependence (*DSM-IV*) along with a separate query for craving status in the previous 30-day period. These data were subsequently combined during analysis to classify CUD based on the current *DSM-5* nosology. In addition to reporting CUD symptoms in the diagnostic interview, participants also reported the age of onset for CUD symptoms in order to control for developmental timing of symptoms. Participants also completed a battery of measures to characterize multiple aspects of cannabis and other substance use across groups. Cannabis use frequency was quantified using a 30-day timeline followback calendar (Sobell, Brown, Leo, & Sobell, 1996;