Psychiatric Comorbidity of Cannabis Use Disorder

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Abstract

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Objective: This chapter reviews the epidemiology and treatment of cannabis use disorder (CUD) with psychiatric comorbidity.

Methods: We summarize the findings of English-language epidemiological studies reporting current (past-year) comorbidity and of controlled clinical trials of treatment in which the majority of participants had diagnosed CUD and a specific comorbid disorder.

Results: There is substantial CUD comorbidity among community-dwelling adults with major psychiatric disorders: 4–6% for depression, 14% for bipolar disorder, 5% for anxiety disorder, and 16% for schizophrenia. Conversely, there is substantial psychiatric comorbidity among community-dwelling adults with CUD: 18–32% for depression, 8–9% for bipolar disorder, and 23–40% for anxiety disorder. No treatment is proven effective for CUD comorbidity; small-scale trials suggest that combined motivational enhancement therapy/cognitive behavioral therapy focused on both CUD and the psychiatric disorder may be effective. Single, small-scale trials suggest that lithium may be effective for comorbid bipolar disorder and clozapine for comorbid schizophrenia.

Conclusions: CUD with comorbid psychiatric disorders is common, and some behavioral interventions appear efficacious; however, there are no proven effective pharmacological treatments for this disorder.

Keywords

Cannabis use disorder
Cannabis
Marijuana
Comorbidity
Schizophrenia
Depression
Bipolar disorder
Anxiety disorder
Personality disorder
Treatment

Introduction

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Cannabis use disorder (CUD) is among the most prevalent psychoactive substance use disorders (SUDs), with an

estimated 13.1 million individuals worldwide having moderate-severe CUD (cannabis dependence in DSM-IV terms) in 2010 [1]. In the United States, an estimated 4.0 million community-dwelling residents had current (past-year) CUD in 2015, a prevalence rate of 1.5% [2].

Therefore, it is not surprising that CUD often co-occurs with other non-SUD psychiatric disorders [3]. For example, a 2007 nationally representative survey of 8,841 community-dwelling Australians 16–85 years old (2007 National Survey of Mental Health and Wellbeing [NSMHW]) found that 69.8% (standard error [SE] 6.5%) of respondents with current (past 12-month) CUD also had psychiatric comorbidity (affective [major depression, dysthymia, bipolar], anxiety [panic, agoraphobia, social phobia, generalized anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorder], and/or alcohol use disorder), compared with 37.8% (SE 3.5) of current cannabis users without CUD and 15.5% (SE 0.5) of current nonusers of cannabis [4]. The odds ratio (OR) for having any comorbid disorder was 3.8 (95% confidence interval [CI] 1.9–7.6) for current cannabis users with CUD vs. current users without CUD and 0.3 (95% CI 0.2–0.4) for current nonusers vs. current users without CUD [4]. A study of 15.1 million adult (18–65 years old) admissions to US non-federal, acute care community general hospitals between 2007 and 2011 (Nationwide Inpatient Sample [NIS] of the Healthcare Cost and Utilization Project [HCUP]) found that 62.05% (95% CI 60.66–63.43) of the 65,767 inpatients with CUD as their only diagnosed SUD also had another non-SUD psychiatric diagnosis (mood, anxiety, psychotic, adjustment, impulse control, personality, or attention-deficit disorder), compared with 27.28% (95% CI 26.90–27.66) of the 14.7 million inpatients without a CUD diagnosis [5]. A retrospective record review of all 1,814,830 patients admitted to 458 hospitals in New South Wales (NSW), Australia, between July 1, 2006, and June 30, 2007, identified 8,669 (5%) patients with a diagnosis of current CUD, of whom 53.8% had another major psychiatric diagnosis (major depressive disorder, bipolar disorder, anxiety disorder, schizophrenia, personality disorder, or “severe stress disorder”), compared with a 4.2% prevalence of these psychiatric disorders among all patients (OR 17.2, 95% CI 17.4–19.0) [6]. A study of 837 outpatients at Madrid mental health clinics found a 66.2% prevalence of current psychiatric comorbidity among the 135 outpatients with current CUD [7].

Whether this comorbidity is due to a direct causal relationship between disorders (in either direction), to the chance co-occurrence of two common disorders, or to the presence of antecedent risk factors that promote the development of both disorders is often unclear. Few epidemiological studies provide information that might allow causal inference, e.g., odds ratios, for occurrence compared to a relevant reference group that might isolate the influence of CUD itself, such as cannabis users without CUD. Even fewer studies adjust the ORs to account for likely confounding risk factors, e.g., other substance use or SUDs and sociodemographic characteristics. The temporal order of onset of the two disorders provides clinically useful information (e.g., distinguishing between primary and secondary disorders), but this information is rarely available from large-scale epidemiological studies. Genetic and twin studies (e.g., comparing concordance for comorbidity in monozygotic and dizygotic twin pairs) might also be informative, but such studies almost always focus on cannabis use, rather than CUD [8].

CUD psychiatric comorbidity is clinically relevant because its presence is often associated with a poorer prognosis for CUD, the other psychiatric disorder, or both [3]. Clinically significant adverse consequences, such as poor treatment adherence and retention, more severe symptoms, greater functional disability, longer duration of active illness, more frequent occurrence of acute exacerbations, and/or greater rates of hospitalization, have been shown for bipolar disorder [9, 10, 11, 12, 13], depression [14], PTSD [15], and schizophrenia [16, 17].

This chapter reviews the epidemiology and treatment of CUD occurring with comorbid psychiatric disorders (except for other SUDs). For epidemiologic data, we focus on recent large-scale, community-based epidemiological surveys, as these provide the most scientifically rigorous data. The majority of such studies are cross-sectional and so do not provide evidence regarding the causal relationship between the two comorbid disorders. When available, we also present data from large-scale, prospective longitudinal studies which provide information about the incidence of comorbid disorders over a defined period of time. We present data on current, rather than lifetime, diagnoses to minimize the influence of recall bias on findings. We distinguish epidemiologic studies along two dimensions. First, do they report prevalence of the psychiatric disorder among individuals with CUD or prevalence of CUD among

individuals with the psychiatric disorder? Second, are study subjects selected because they live in the community (and, ideally, are selected to be representative of everyone living in that community), regardless of treatment or treatment-seeking status, or are subjects selected because they are in treatment or seeking treatment (i.e., clinical populations)? The latter groups are likely to be enriched with individuals who have comorbid (i.e., two or more) disorders because those with multiple disorders are more likely to be in treatment (the so-called Berkson's bias or paradox) [18]. For treatment data, we focus on controlled clinical trials in which the majority of participants have diagnosed CUD and another specific psychiatric disorder.

This chapter does not cover cannabis use (i.e., without CUD) in the context of other psychiatric disorders, a topic on which there is substantial published literature. CUD comorbidity with schizophrenia (i.e., non-affective psychosis) is covered only briefly, as this topic is dealt with in more detail in the chapter by Drs. Tikka and D'Souza.

Mood Disorders

Epidemiology

Several nationally representative, cross-sectional epidemiological studies suggest substantial bidirectional comorbidity between CUD and mood or affective disorders (e.g., depression, dysthymia, bipolar). A 2012–2013 nationally representative survey of 36,309 non-institutionalized US adults (National Epidemiologic Survey on Alcohol and Related Conditions [NESARC]-III) found a 7.3% (SE 0.51%) prevalence of current (past 12-month) CUD among respondents with any current mood disorder (major depressive disorder, persistent depression, or bipolar disorder), compared with 2.5% in the general population [19]. The adjusted odds ratio (aOR) for current CUD among respondents with current mood disorder (compared to those without a current psychiatric disorder) was 3.8 (adjusted for sociodemographic characteristics, 95% CI 3.10–4.56). Viewing comorbidity from the opposite direction, the NESARC-III study found a 33.3% (SE 2.76%) prevalence (aOR 1.9 [adjusted for sociodemographic characteristics and other psychiatric disorders], 95% CI 1.34–2.64) of any current mood disorder among men with current CUD and 48.9% (3.46%) prevalence (aOR 1.5, 95% CI 1.05–2.23) among women [20]. The US NIS study found that 41.00% (95% CI 39.94–42.08) of adults hospitalized between 2007 and 2011 with CUD as their only SUD diagnosis also had a mood disorder diagnosis, compared with 19.49% (95% CI 19.18–19.80) of inpatients without a CUD diagnosis [5] . The 2007 Australian NSMHW found a similarly high rate of comorbidity: the prevalence of any current affective disorder (major depressive disorder, dysthymia, bipolar) was 36.9% (SE 8.1%) among respondents with current CUD, compared with 5.6% (0.3%) among current nonusers of cannabis and 12.5% (2.2%) among current cannabis users without current CUD [4]. The OR for having a comorbid affective disorder among respondents with current CUD, compared to current cannabis users without current CUD, was 3.0 (95% CI 1.4–6.6).

A similar finding of substantial comorbidity was found in a national registry study of 22,615 patients who entered treatment for a SUD in a publicly funded treatment facility in Chile between 2007 and 2013 [21]. Among the 1,265 patients with CUD as their only current illicit SUD, 13.2% (95% CI 11.4–15.2) had a current affective disorder (aOR 1.58 [adjusted for sociodemographic characteristics and alcohol use], 95% CI 1.30–1.92), compared to the 9.3% (95% CI 8.7–9.9) prevalence among the 9,526 patients with cocaine as their only current illicit SUD. The 11,824 patients with comorbid CUD and cocaine use disorder also had a significantly lower 8.7% (95% CI 8.2–9.2) prevalence of current affective disorder (aOR 1.07, 95% CI 0.96–1.12) compared to patients with cocaine use disorder only.

Mood disorders are associated with the development of CUD by cannabis users. A secondary analysis of data collected in the 2001–2002 NESARC study from a representative sample of 43,093 non-institutionalized US adults found that lifetime cannabis users with a mood disorder were significantly more likely to have CUD than were lifetime users without any psychiatric disorder (aOR 3.9 [adjusted for sociodemographic characteristics], 95% CI 2.8–5.3) [22].

Depression

Epidemiology

Large-scale, nationally representative epidemiological surveys of community-dwelling adults in several countries show substantial comorbidity between CUD and depression. The 2012–2013 NESARC-III study in the United States found the prevalence of current CUD among those with a current depressive disorder to be 6.2% (SE 0.49%) for major depressive disorder (aOR 2.8, 95% CI 2.33–3.41) and 7.8% (1.11%) for persistent depression [19]. A nationally representative survey of 39,133 non-institutionalized US adults (2011 National Survey on Drug Use and Health [NSDUH]) found a 4.11% (95% CI 3.15–5.08) prevalence of current CUD among respondents with current major depressive episode, compared with a 1.18% (95% CI 1.06–1.31) prevalence among respondents without current major depressive episode [23]. A nationally representative 2012 survey of 25,113 non-institutionalized Canadians age 15 years or older (Canadian Community Health Study—Mental Health) found a 5.4% (95% CI 0.9–5.0) prevalence of current CUD among respondents with current major depressive disorder, compared with a 1.1% (95% CI 0.3–0.9) prevalence among respondents without current major depressive disorder [24]. Conversely, the NESARC-III study found a 20.3% (SE 2.11%) prevalence of current major depressive disorder (aOR 1.3, 95% CI 0.94–1.79) and 9.2% (SE 1.70%) prevalence of persistent depression (aOR 1.9, 95% CI 1.09–3.30) among men with current CUD [20]. Among women with current CUD, the corresponding figures were 35.7% (SE 3.24%) prevalence of major depressive disorder (aOR 1.2, 95% CI 0.85–1.76) and 10.2% (SE 2.10%) prevalence of persistent depression (aOR 1.0, 95% CI 0.50–1.89). A secondary analysis of nationally representative survey data from 340,456 non-institutionalized US adults interviewed between 2005 and 2013 (NSDUH) found an 18.25% (SE 0.61) prevalence of past-year major depressive episode among the 10,795 respondents with past-year CUD [25]. The prevalence of major depressive episode was significantly lower among the 1,841 African-Americans with CUD (13.80%, 95% CI 11.39–16.63) and significantly higher among the 489 respondents who self-reported as “mixed race” (29.02%, 95% CI 19.80–40.38). The 2007 Australian NSMHW study found a 32.4% (SE 8.0%) prevalence of current major depressive disorder and 10.8% (SE 5.9%) prevalence of dysthymia among respondents with current CUD [4]. The ORs, compared with current cannabis users without current CUD, were 2.3 (95% CI 0.7–7.6) for major depressive disorder and 0.9 (95% CI 0.1–9.5) for dysthymia, suggesting that cannabis use, rather than CUD itself, is a significant risk factor for having depression. Also consistent with this interpretation is a meta-analysis including 14 published longitudinal studies of cannabis use and depression involving 76,058 participants [26]. The OR for heavy cannabis users (CUD or at least weekly use) subsequently developing depression (controlling for presence of depression at baseline) was 1.62 (95% CI 1.21–2.16) compared with light users (less than weekly) or nonusers. The OR for all users compared with nonusers was lower (1.17, 95% CI 1.05–1.30).

Similar patterns of comorbidity are found in large-scale studies of patients with a history of psychiatric treatment. The NSW hospital study found a 10.9% prevalence of major depressive disorder among patients hospitalized with CUD (OR 8.7, 95% CI 8.1–9.3) [6]. A Danish cohort study of 197,057 individuals treated for depression from 1969 to 2014 (derived from several national population-based registries) found a 2.1% prevalence of comorbid CUD [27]. A Norwegian cohort study of 87,540 patients born between 1950 and 1989 and treated for depression between 2009 and 2014 (derived from the Norwegian Patient Registry) found a 2.0% 5-year prevalence of CUD [28]. The Madrid mental health clinic study found a 19.5% prevalence of current major depressive episode among the 135 outpatients with current CUD and a 14.3% prevalence of current dysthymia [7].

Two community-based, prospective, longitudinal epidemiological studies shed light on the relationship between CUD and depression. A study that interviewed 1,920 non-institutionalized adults in the Baltimore, MD, metropolitan area in 1980 (Baltimore Epidemiologic Catchment Area [ECA] study) and re-interviewed them 14–16 years later found that, among those without depressive symptoms at baseline, presence of CUD at baseline made it significantly more likely to have depressive symptoms at follow-up than among respondents without baseline CUD (OR 4.00, 95% CI 1.23–12.97) [29]. Conversely, among respondents without CUD at baseline, presence of depressive symptoms at baseline was not associated with increased prevalence of CUD at follow-up, either with or without adjustment for age, sex, and presence of other SUDs. A study that interviewed 43,093 non-institutionalized US adults in 2001–2002 and re-interviewed 34,653 of them 3 years later (NESARC waves I and II) found that, among those without major depressive disorder at baseline, respondents with CUD at baseline were significantly more likely to have major

depressive disorder at follow-up than were those without CUD or alcohol use disorder at baseline (OR 2.02, 95% CI 1.35–3.04) [30]. Conversely, among those without CUD at baseline, respondents with major depressive disorder at baseline were significantly more likely to have CUD at follow-up than those without baseline major depressive disorder (OR 5.23, 95% CI 1.28–21.34).

Treatment

Adults with comorbid depression and CUD may be more likely to seek treatment than those with only CUD, as would be expected from Berkson's bias. A secondary analysis of data from the 2005 to 2013 US NSDUH found that respondents with comorbidity were significantly more likely to have used cannabis-related treatment services in the past year than were respondents without a major depressive episode within the past year (aOR 1.74 [adjusted for sociodemographic characteristics and presence of other SUDs], 95% CI 1.29–2.34) [25].

There are relatively few published clinical trials of treatment for comorbid CUD and depression; many studies include cannabis users but do not provide a specific use disorder diagnosis [31, 32, 33]. A small controlled clinical trial in Australia randomly assigned 97 adults with comorbid major depressive disorder and "problematic" cannabis (71%) and/or alcohol (54%) use to either brief intervention (one motivational interview followed by no further treatment) or to 10 weekly sessions of combined motivational interviewing/cognitive behavioral therapy (CBT), delivered either in person or via computer [34]. Combined treatment was significantly more effective than brief intervention in reducing depressive symptoms and cannabis-related problems over the 12-month follow-up period, with computer-administered therapy showing the largest treatment effect.

Three controlled clinical trials of antidepressants (fluoxetine, venlafaxine) for the treatment of comorbid CUD and depression found mixed evidence of efficacy. A controlled clinical trial that randomized 70 adolescents/young adults (15–25 years old) with comorbid major depression and CUD to receive 12 weeks of manual-based motivation enhancement therapy (MET) and CBT plus either fluoxetine (20 mg daily) or placebo found no significant benefit from fluoxetine; both treatment groups showed comparable significant decreases in depressive symptoms, cannabis-related problems, and frequency of cannabis use [35], with comparable improvement in both groups persisting at 1-year follow-up [36]. The investigators attributed fluoxetine's lack of efficacy to the robust effect of CBT. An earlier clinical trial by the same research group that evaluated a subgroup of 22 adults with CUD and comorbid major depression and alcohol use disorder (from among 51 adults with comorbid major depression and alcohol use disorder) randomized to 12 weeks of weekly supportive psychotherapy plus fluoxetine (20–40 mg daily) or placebo found that fluoxetine significantly reduced depressive symptoms and the quantity and frequency of cannabis use [37]. A controlled clinical trial that randomly assigned 103 adults with comorbid CUD and major depressive disorder or dysthymia to 12 weeks of manual-based weekly CBT plus either venlafaxine-extended release (up to 375 mg daily) or placebo found venlafaxine associated with significantly lower likelihood of achieving abstinence (11.8% vs. 36.5%); both treatment groups had comparable significant improvement in depression [38].

Bipolar Disorder

Epidemiology

A systematic review and meta-analysis of 9 published community-based epidemiological surveys involving 218,397 respondents found a prevalence of around 20% for current CUD among respondents with bipolar disorder (including bipolar I disorder) and a prevalence of around 10% for bipolar disorder among respondents with current CUD [39]. A systematic review and meta-analysis by the same research group that included 78 published studies of clinical populations (both inpatient and outpatient) found similar rates of comorbidity, in both directions [40]. For example, the 2012–2013 NESARC-III study in the United States found the prevalence of current CUD among those with current bipolar disorder to be 14.6% (SE 1.64) for bipolar I disorder (aOR 5.0, 95% CI 3.65–6.75) and 2.7% (1.10–6.62%) for bipolar II disorder (aOR 2.7, 95% CI 1.10–6.62) [19]. Conversely, the NESARC-III study found a 8.8% (SE 1.44%)

prevalence of current bipolar I disorder (aOR 1.6, 95% CI 0.93–2.59) and 0.8% (SE 0.41%) prevalence of current bipolar II disorder (aOR 0.9, 95% CI 0.28–3.07) among men with current CUD [20]. Among women with current CUD, the corresponding figures were 9.0% (SE 1.69%) prevalence of current bipolar I disorder (aOR 1.3, 95% CI 0.75–2.18) and 1.5% (SE 0.89%) prevalence of current bipolar II disorder (aOR 1.3, 95% CI 0.32–5.40). The 2007 Australian NSMHW study found a 7.8% (SE 3.3%) prevalence of current bipolar disorder among respondents with current CUD [4]. The OR, compared with current cannabis users without current CUD, was 1.5 (95% CI 0.2–8.7), suggesting the CUD itself is not a significant risk factor for having bipolar disorder.

Similar patterns of comorbidity are found in large-scale studies of patients with a history of psychiatric treatment. The NSW hospital study found a 5.7% prevalence of bipolar disorder among inpatients with CUD (OR 17.6, 95% CI 16.0–19.4) [6]. A Danish cohort study of 24,567 individuals treated for bipolar disorder from 1969 to 2014 (derived from several national population-based registries) found a 3.3% prevalence of comorbid CUD [27]. A Norwegian cohort study of 15,540 patients born between 1950 and 1989 and treated for bipolar disorder between 2009 and 2014 (derived from the Norwegian Patient Registry) found a 3.3% 5-year prevalence of CUD [28]. The Madrid mental health clinic study found a 29.3% prevalence of current bipolar disorder among the 135 outpatients with current CUD [7].

Treatment

A recent review of treatment for bipolar disorder and comorbid SUD concluded that integrated psychosocial treatment incorporating elements of MET and CBT with components targeted to both disorders was more effective than generic 12-step enhancement or counseling, based on a limited number of small clinical trials [41]. However, the review did not identify any studies specifically focused on CUD.

A controlled clinical trial that randomly assigned 25 adolescents with a mood or anxiety disorder or ADHD (70% with bipolar disorder) and comorbid SUD (56% CUD + alcohol use disorder, 8% CUD only) to receive 6 weeks of weekly interpersonal therapy plus lithium (targeted to serum level of 0.9 meq/L) or placebo found that lithium significantly reduced mood symptoms and substance use (assessed with urine toxicology screens) [42].

Anxiety Disorders

A meta-analysis of 11 published epidemiological studies (cross-sectional or prospective cohort) involving non-institutionalized individuals found a significant association between anxiety disorders and CUD (OR 1.87, 95% CI 1.43–2.44 for those with vs. without CUD) [43]. The 2012–2013 NESARC-III study in the United States found the prevalence of current CUD among those with a current anxiety disorder to be 5.4% (SE 0.46) (aOR 2.8, 95% CI 2.24–3.39) [19]. For specific anxiety disorders, the prevalence of current CUD was 6.9% (SE 1.35) (aOR 2.6, 95% CI 1.64–4.06) for agoraphobia, 7.1% (SE 0.85) (aOR 3.7, 95% CI 2.79–5.02) for generalized anxiety disorder, 8.3% (SE 1.05) (aOR 3.3, 95% CI 2.50–4.48) for panic disorder, 6.3% (SE 0.99) (aOR 2.3, 95% CI 1.61–3.27) for social anxiety disorder (social phobia), and 4.0% (SE 0.54) (aOR 1.7, 95% CI 1.28–2.29) for any specific phobia [19]. Conversely, the NESARC-III study found a 23.4% (SE 2.3) prevalence of any current anxiety disorder (aOR 1.2, 95% CI 0.88–1.56) among men with current CUD [20]. Among women with current CUD, the corresponding figure was 36.1% (SE 3.74) (aOR 0.8, 95% CI 0.58–1.23). Among men, the prevalence of specific anxiety disorders among those with current CUD was 1.6% (SE 0.50) (aOR 0.3, 95% CI 0.16–0.73) for agoraphobia, 12.2% (SE 1.88) (aOR 1.2, 95% CI 0.79–1.92) for generalized anxiety disorder, 7.4% (SE 1.20) (aOR 1.3, 95% CI 0.83–2.10) for panic disorder, and 7.3% (CI 0.66–1.55) for any specific phobia. The corresponding figures for women were 9.0% (SE 2.11) (aOR 1.3, 95% CI 0.67–2.79) for agoraphobia, 19.9% (SE 3.19) (aOR 1.3, 95% CI 0.83–2.19) for generalized anxiety disorder, 15.2% (SE 2.81) (aOR 0.9, 95% CI 0.50–1.57) for panic disorder, 7.2% (SE 1.76) (aOR 0.6, 95% CI 0.32–1.04) for social anxiety disorder, and 9.9% (SE 1.93) (aOR 0.5, 95% CI 0.32–0.87) for any specific phobia. These findings suggest a unidirectional pattern of comorbidity for anxiety disorders and CUD: CUD has a greater than chance association with anxiety disorder (reflected in ORs significantly greater than 1), while anxiety disorders don’t have a significant

association with CUD.
AQ3

The 2007 Australian NSMHW study found a 40.5% (SE 7.7) prevalence of any current anxiety disorder among respondents with current CUD, compared with 20.8% (SE 2.1) among current cannabis users without CUD and 11.2% (SE 0.5) among current nonusers [4]. The OR for having any anxiety disorder was 1.1 (95% CI 0.6–2.2) for current cannabis users with CUD vs. current users without CUD and 0.7 (95% CI 0.5–0.9) for current nonusers vs. current users without CUD. For specific anxiety disorders, the prevalence among those with current CUD was 5.2% (SE 2.7) for agoraphobia (OR 2.2, 95% CI 0.4–12.8 vs. current users without CUD; OR 1.8, 95% CI 0.6–5.0 for nonusers vs. users), 19.0% (SE 6.7) for generalized anxiety disorder (OR 1.7, 95% CI 0.5–6.4 vs. current users without CUD; OR 1.3, 95% CI 0.6–2.5 for nonusers vs. users), 7.4% (SE 5.7) for panic disorder (OR 0.9, 95% CI 0.0–33.6 vs. current users without CUD; OR 0.8, 95% CI 0.3–1.8 for nonusers vs. users), and 14.0% (SE 3.8) for social phobia (OR 0.9, 95% CI 0.3–2.8 vs. current users with CUD; OR 0.8, 95% CI 0.5–1.3 for nonusers vs. users). These findings suggest that cannabis use, but not CUD itself, is a significant risk factor for anxiety disorder.

A prospective longitudinal study that followed almost 35,000 non-institutionalized US adults over 3 years starting in 2001–2002 (NESARC-I waves 1 and 2) found no significant associations between CUD and anxiety disorders, either with or without adjustment for sociodemographic characteristics and other psychiatric disorders [44]. Among respondents with CUD (but no anxiety disorder) at baseline (n = 319), there was no increased prevalence of any anxiety disorder at 3-year follow-up (aOR 0.99, 95% CI 0.65–1.5) nor of any specific anxiety disorder: generalized anxiety disorder (aOR 1.08, 95% CI 0.61–1.93), panic disorder (aOR 1.69, 95% CI 0.88–3.25), social anxiety disorder (aOR 1.75, 95% CI 0.95–3.23), or any specific phobia (aOR 0.71, 95% CI 0.43–1.15). Conversely, among respondents with any anxiety disorder (but no CUD) at baseline, there was no increased prevalence of CUD at 3-year follow-up (aOR 0.68, 95% CI 0.41–1.14). This was also true for each specific anxiety disorder.

Large-scale studies of patients with a history of psychiatric treatment do find substantial comorbidity between CUD and anxiety disorders. The US NIS study found that 12.54% (95% CI 12.00–13.11) of adults hospitalized between 2007 and 2011 with CUD as their only SUD diagnosis also had an anxiety disorder diagnosis, compared with 7.47% (95% CI 7.34–7.61) among patients without a CUD diagnosis [5]. The NSW hospital study found a 3.4% prevalence of anxiety disorder among inpatients with CUD (OR 4.8, 95% CI 4.3–5.5) [6]. A Danish cohort study of 40,552 individuals treated for anxiety disorder from 1969 to 2014 (derived from several national population-based registries) found a 2.9% prevalence of comorbid CUD [27]. The Madrid mental health clinic study found a 23.3% prevalence of current anxiety disorder among the 135 outpatients with current CUD, a 15.8% prevalence of current agoraphobia, and a 10.5% prevalence of current social phobia [7].

Treatment

We are not aware of any published controlled clinical trials of treatment for CUD with a comorbid anxiety disorder. An open-label case series involving 59 adults with comorbid social anxiety disorder and SUDs (38% CUD, 73% alcohol use disorder, 32% opiate use disorder, 29% cocaine use disorder) found that 10 weeks of weekly group CBT targeted at both anxiety and substance use produced significant reductions in social anxiety-related symptoms and negative affect [45]. Data on cannabis use were not reported.

Post-traumatic Stress Disorder (PTSD)

Epidemiology

Several nationally representative, community-based epidemiological surveys show comorbidity between CUD and PTSD. The 2012–2013 NESARC-III study in the United States found the prevalence of current CUD among those with current PTSD to be 9.4% (SE 0.94) (aOR 4.3, 95% CI 3.15–4.67) [19]. Conversely, the NESARC-III study found a 12.3% (SE 1.66) prevalence of current PTSD (aOR 1.7, 95% CI 1.12–2.57) among men with current CUD [20].

Among women with current CUD, the corresponding figure was 26.9% (SE 3.37) (aOR 1.6, 95% CI 1.01–2.48). The 2007 Australian NSMHW study found a 9.4% (SE 3.8) prevalence of PTSD among respondents with current CUD, compared with 8.1% (SE 1.8) among current cannabis users without CUD and 4.1% (SE 0.3) among current nonusers [4]. The ORs for having PTSD were not significantly different from 1 for current cannabis users with CUD vs. current users without CUD (OR 0.5, 95% CI 0.1–2.2) or for current nonusers vs. current users without CUD (OR 0.7, 95% CI 0.4–1.3).

Large-scale studies of patients with a history of psychiatric treatment also find substantial comorbidity between CUD and PTSD. A Danish cohort study of 7,343 individuals treated for PTSD from 1969 to 2014 (derived from several national population-based registries) found a 3.0% prevalence of comorbid CUD [27]. The Madrid mental health clinic study found a 4.5% prevalence of current PTSD among the 135 outpatients with current CUD [7].

Treatment

A recent systematic review and meta-analysis including 14 studies (involving 1,506 participants) of psychosocial treatment for PTSD and comorbid SUD found that individual therapies combining trauma-focused and SUD-focused components overall produced significantly more reduction in PTSD symptoms than single-component therapies but did not significantly reduce substance use [46]. However, few of these studies included substantial numbers of cannabis users, and none explicitly included participants with CUD.

A controlled clinical trial randomly assigned 44 adult women prisoners with PTSD and comorbid alcohol use disorder, 75% of whom were also heavy cannabis users, to receive 6–8 weeks of psychoeducational groups and individual drug counseling (based on a 12-step model) with or without a CBT module based on safety-seeking before discharge from a minimum-security residential facility [47]. There were no significant group differences in PTSD symptoms or substance use at 3- and 6-month follow-up, but there was a significant positive association between number of CBT sessions and reduction in PTSD symptoms and drug use. A small open-label trial involving 37 adolescents with PTSD and current substance use (but not necessarily a SUD) (81% cannabis users) found that 12 weeks of manualized group CBT with both trauma- and substance use-focused components was associated with significant reductions from baseline to end of treatment in PTSD and depressive symptoms and proportion of days of cannabis use (decreasing from 16% to 9%) [48]. Another controlled clinical trial involving adults with comorbid PTSD and SUDs randomized to 6 weeks of twice weekly individual CBT sessions targeted to both PTSD and SUD or SUD alone recently completed enrollment [49].

We are not aware of any published studies of pharmacological treatment of comorbid CUD and PTSD.

Obsessive–Compulsive Disorder (OCD)

Epidemiology

The 2007 Australian NSMHW study found a 19.9% (SE 7.4) prevalence of OCD among respondents with current CUD, compared with 4.6% (SE 1.2) among current cannabis users without CUD and 2.4% (SE 0.2) among current nonusers [4]. The ORs for having OCD were not significantly different from 1 for current cannabis users with CUD vs. current users without CUD (OR 2.3, 95% CI 0.6–8.7) or for current nonusers vs. current users without CUD (OR 0.8, 95% CI 0.4–1.6). A Danish cohort study of 5,953 individuals treated for OCD from 1969 to 2014 (derived from several national population-based registries) found a 2.3% prevalence of comorbid CUD [27]. The Madrid mental health clinic study found an 8.3% prevalence of current OCD among the 135 outpatients with current CUD [7].

Treatment

We are not aware of any studies on the treatment of comorbid CUD and OCD.

Schizophrenia

Epidemiology

There are relatively few community-based epidemiological studies that provide data on CUD comorbidity with schizophrenia, in part because the lifetime prevalence of schizophrenia in the general population is estimated at only 5.5 (SD 4.5) per 1,000 [50]. A nationally representative 2001–2002 survey of 43,093 non-institutionalized US adults (NESARC-I) found that 7.9% (95% CI 3.2–12.6) of respondents with lifetime schizophrenia (based on self-report of receiving this diagnosis from a doctor) also had a lifetime diagnosis of CUD [22]. The aOR (adjusted for sociodemographic characteristics) for a CUD diagnosis among respondents with schizophrenia and cannabis use (compared to cannabis users without any psychiatric disorder) was 0.8 (95% CI 0.1–4.0), suggesting that the presence of comorbid schizophrenia does not significantly enhance the transition from cannabis use to CUD. A nationally representative 1997 survey of 6,722 community-dwelling Australian adults (18–50 years old) (1997 NSMHWB) found a 16.2% prevalence of current CUD among the 99 respondents with current schizophrenia or schizoaffective disorder, compared with a 3.3% prevalence among respondents without schizophrenia (OR 5.86, 95% CI 3.37–10.18) [51]. A 2002 survey of 8,484 Britons (16–74 years old) living in households found a 6.9% prevalence of current CUD among the 68 respondents with current psychosis, compared with a 2.5% prevalence among respondents without current psychosis (OR 2.92, 95% CI 1.05–8.13) [52].

A systematic review and meta-analysis that included 10 published studies of patients in treatment found a median prevalence of 16.0% (interquartile range 8.6–28.6) for current CUD among patients with schizophrenia, with higher prevalence among first-episode patients than chronic patients (28.6% vs. 22.0%) and among younger than older patients (38.5% vs. 16.0%) [16]. Several more recent national studies of patients in treatment also find substantial comorbidity between CUD and schizophrenia. The US NIS study found that 19.51% (95% CI 18.48–20.58) of 65,767 adults hospitalized between 2007 and 2011 with CUD as their only SUD diagnosis also had a diagnosis of schizophrenia, psychosis, or delusional disorder, compared with a 3.94% (95% CI 3.76–4.12) prevalence among inpatients without a CUD diagnosis [5]. The NSW hospital study found a 15.0% prevalence of schizophrenia among inpatients with CUD (OR 34.8, 95% CI 32.7–37.0) [6]. A Danish cohort study of 53,035 individuals treated for schizophrenia from 1969 to 2014 (derived from several national population-based registries) found a 13.2% prevalence of comorbid CUD [27]. A Norwegian cohort study of 9,002 patients born between 1950 and 1989 and treated for schizophrenia between 2009 and 2014 (derived from the Norwegian Patient Registry) found a 6.7% 5-year prevalence of CUD [28].

Two large-scale studies of patients in treatment compared comorbidity prevalence in those with CUD only, a stimulant use disorder only, and both disorders. An Australian study of 13,624 adults (18–50 years old) admitted to public hospitals in New South Wales between 2000 and 2011 with a diagnosis of schizophrenia and who had at least 2 years of treatment within the subsequent 5 years found a 17.8% prevalence of CUD and 11.2% prevalence of CUD + stimulant use disorder, compared with a 2.8% prevalence among patients with stimulant use disorder only [17]. Patients with comorbid CUD only were significantly more likely to be men (OR 2.2, 95% CI 2.0–2.5) and younger than age 46 years (e.g., OR 2.0, 95% CI 1.6–2.6 for those 36–40 years old). The Chilean national registry study of patients entering addiction treatment between 2007 and 2013 found a 5.2% (95% CI 4.1–6.6) prevalence of schizophrenia and related psychoses among patients with CUD only, compared with 2.3% (95% CI 2.1–2.6) among patients with CUD + cocaine use disorder and 1.1% (95% CI 0.9–1.4) prevalence among patients with cocaine use disorder only (aOR 4.32, 95% CI 3.03–6.18) [21]. Patients with comorbid CUD + cocaine use disorder also had a significantly greater prevalence of schizophrenia than patients with cocaine use disorder only (aOR 1.92, 95% CI 1.52–2.42) but significantly lower than patients with CUD only. These findings suggest that comorbid schizophrenia is more strongly associated with CUD than with stimulant use disorder, even though acute intoxication with both types of drugs is associated with psychosis.

Treatment

The larger literature on cannabis use by individuals with schizophrenia and related disorders suggests that psychosocial treatment may reduce cannabis use and positive symptoms of schizophrenia [53, 54, 55, 56]. However, findings from the small number of controlled clinical trials of psychosocial treatment involving adults with comorbid CUD and schizophrenia and related disorders suggest little or no benefit from CBT and MET. A controlled clinical trial (CapOpus) in Denmark involving 103 adults with comorbid CUD and psychosis (51% schizophrenia, 31% schizotypal disorder) who were randomized to 6 months of treatment as usual (medication and CBT focused on psychosis) without or with weekly CBT/motivational interviewing focused on cannabis use found that psychosocial treatment did not significantly reduce the self-reported frequency of cannabis use at end of treatment or 4-month follow-up [57]. Over the subsequent 4-year period, participants who received the cannabis-focused psychosocial treatment had more psychiatric hospital admissions (incidence rate ratio 2.24, 95% CI 1.65–3.03) and more psychiatric emergency room contacts (incidence rate ratio 3.47, 95% CI 2.64–4.57) than those who received only treatment as usual, based on the Danish Psychiatric Central Research Register [58].

A controlled clinical trial in Ireland involving 88 adults with comorbid cannabis dependence and early onset (within 3 years) psychosis (55% with schizophrenia, schizoaffective disorder, or schizophreniform psychosis) who were randomized to 12 weeks of treatment as usual (multidisciplinary team providing antipsychotic treatment) without or with weekly CBT and motivational interviewing focused on cannabis use found the psychosocial treatment associated with better subjective quality of life at 3-month and 1-year follow-up, but no difference in cannabis use or psychosis symptoms [59].

A controlled clinical trial in Australia involving 130 adults with comorbid current SUD (73% CUD, 67.3% alcohol, 42% amphetamine) and psychotic disorder (62% schizophrenia, 12.6% schizoaffective disorder) who were randomized to treatment as usual (self-help booklet about substance use) without or with 10 weeks of weekly motivational interviewing/CBT focused on substance use found that the psychosocial treatment significantly decreased self-reported frequency of cannabis use at 15 weeks, with no significant difference at 6 months or 12 months [60]. There was no difference in cannabis abstinence rates at any time point. The psychosocial treatment modestly reduced depressive symptoms and improved overall functioning, but had no effect on positive or negative symptoms of schizophrenia.

A controlled clinical trial in the United States involving 31 adults with comorbid schizophrenia and CUD (77%) and/or alcohol use disorder (77%) randomized to usual care or 18 months of cognitive enhancement therapy (individual, group, and computer-based sessions focused on goal setting, motivation for treatment, stress and emotion management, and improving social interactions, plus psychoeducation on substance use and schizophrenia) found that the psychosocial treatment significantly improved social adjustment and emotional function and significantly reduced frequency of self-reported alcohol use, but had no effect on cannabis use [61].

Findings from several small controlled clinical trials of antipsychotic medication treatment of comorbid CUD and schizophrenia suggest little or no benefit, with the possible exception of clozapine [53, 62]. A controlled clinical trial involving 31 adults with comorbid CUD and schizophrenia or schizoaffective disorder who were randomly assigned to 12 weeks of continuing their current antipsychotic medication or switching to clozapine (400–550 mg/day) found that clozapine significantly decreased cannabis use (by about 4.5 joints/week) but had no significant effect on schizophrenia symptoms or overall functioning [63]. A clinical trial involving 30 adults with comorbid CUD and schizophrenia, schizoaffective disorder, or schizophreniform disorder who were openly randomized to 12 months of clozapine (50–425 mg daily) or ziprasidone (80–400 mg daily) found that both treatment groups had comparable significant reductions in cannabis use, with clozapine producing greater reduction in positive symptoms of schizophrenia and more side effects (primarily hypersalivation) [64]. A controlled clinical trial involving 28 adults with comorbid SUD (93% CUD, 79% cocaine use disorder) and schizophrenia or schizoaffective disorder who were randomized to 10 weeks of risperidone (9 mg/day) or olanzapine (20 mg/day) found no significant change in cannabis use (proportion of THC-negative urine samples) in either treatment group [65].

Two open-label within-subject trials conducted by the same research group in Montreal, Canada, found some benefit in patients with comorbid schizophrenia-spectrum disorders switched from another antipsychotic medication (not clozapine) to 12 weeks of quetiapine (200–800 mg daily). The first trial, involving 24 adults with comorbid schizophrenia (58%), schizoaffective disorder (33%), or schizophreniform disorder (8%) and SUDs (63% CUD, 42% alcohol, 33% stimulants, 38% poly-substance use), found a significant decrease in self-reported cannabis use and craving, but no change in proportion of cannabis-positive urine tests [66]. The second trial, involving 26 adults with comorbid schizophrenia (58%), schizoaffective disorder (35%), or schizophreniform disorder (8%) and SUDs (58% CUD, 46% alcohol, 35% stimulants, 38% poly-substance use), found a significant decrease in self-reported substance use and severity of substance dependence (based on DSM-IV dependence criteria), as well as decreased positive and negative symptoms of schizophrenia [67]. These findings should be interpreted cautiously because of the weak study design and potential for quetiapine itself to be abused [68].

Attention-Deficit/Hyperactivity Disorder

Epidemiology

A 2004–2005 study of 33,488 non-institutionalized US adults (NESARC-I, wave 2) found about a 30% prevalence of lifetime CUD (varying by attention-deficit/hyperactivity disorder [ADHD] subtype: inattentive, hyperactive-impulsive, or combined) among the 965 respondents with ADHD, compared with 5% among the 15,614 respondents without ADHD or ADHD-type symptoms (aOR 2.14 [adjusted for socioeconomic characteristics, conduct disorder, major depression, and anxiety disorder], 95 CI 1.58–2.90) [69]. The 17,009 respondents with ADHD-type symptoms (but not meeting full DSM-IV diagnostic criteria for ADHD) also had significantly greater prevalence of lifetime CUD (10%; aOR 1.29, 95% CI 1.20–1.38). A 2010–2011 study of 5,103 male Swiss Army conscripts found a 21.9% prevalence of current CUD among the 215 conscripts with current ADHD, compared with an 8.0% prevalence among conscripts without current ADHD (chi-square 48.43, $P < 0.001$) [70].

The US NIS study found a 2.82% (95% CI 2.64–3.01) prevalence of attention-deficit, conduct, or disruptive behavior disorder diagnosis among the 65,767 inpatients with CUD as their only SUD diagnosis, compared with a 0.63% (95% CI 0.61–0.65) prevalence among inpatients without any CUD diagnosis [5]. Conversely, a study of 1205 adults seeking treatment for SUD in 7 European countries (International ADHD in Substance Use Disorders Prevalence [IASP] Study) found a 22% prevalence of ADHD among the 129 respondents with CUD (OR 1.7, 95% CI 1.0–2.9) [71].

A meta-analysis of nine published prospective, longitudinal studies found that children with ADHD were significantly more likely to have CUD at follow-up (as adolescents/young adults) than those who did not have childhood ADHD (OR 1.58, 95% CI 1.16–2.14) [72]. However, a prospective longitudinal study of 1,512 11-year-old twins (Minnesota Twin Family Study) found no significant association between lifetime ADHD at study entry and CUD at age 18 years (aOR 0.58 [adjusted for conduct disorder], 95% CI 0.28–1.20) [73]. This finding suggests that some of the observed associations between CUD and ADHD may be confounded by comorbid conduct disorder.

Treatment

A controlled clinical trial that randomized 46 adults with comorbid cannabis dependence and ADHD (DSM-IV criteria) to 12 weeks of treatment with atomoxetine (80–100 mg daily) or placebo found that atomoxetine significantly reduced some ADHD symptoms, but had no significant effect on cannabis use [74].

Impulse Control Disorders

Epidemiology

We are aware of only two epidemiological studies that provide data on the comorbidity of CUD and impulse control

disorders, both of which found a significant association between CUD and impulse control disorders (although without controlling for potential confounds). A reanalysis of data from a 2001–2002 nationally representative survey of 9,282 community-dwelling US adults (National Comorbidity Survey Replication [NCS-R]) found a current CUD prevalence of 7.2% among the 207 respondents with current intermittent explosive disorder (applying DSM-5 diagnostic criteria), compared with a prevalence of 0.6% among respondents without current intermittent explosive disorder (OR 6.65, 95% CI 3.58–12.35) [75]. The US NIS study found a 1.15% (95% CI 1.03–1.28) prevalence of any impulse control disorder diagnosis among the 65,767 inpatients with CUD as their only SUD diagnosis, compared with a 0.16% (95% CI 0.14–0.17) prevalence among inpatients without any CUD diagnosis [5].

Treatment

We are not aware of any published clinical trials of treatment for comorbid CUD and impulse control disorders.

Personality Disorders

Epidemiology

The 2012–2013 NESARC-III study in the United States found the prevalence of current CUD among those with a current personality disorder to be 8.6% (SE 0.46) (aOR 4.8, 95% CI 3.96–5.75) [19]. For specific personality disorders, the prevalence of current CUD was 11.2% (SE 0.75) (aOR 4.0, 95% CI 3.46–4.72) for schizotypal, 9.5% (SE 0.56) (aOR 4.5, 95% CI 3.96–5.19) for borderline, and 11.7% (SE 0.87) (aOR 4.7, 95% CI 4.07–5.34) for antisocial personality disorder (ASPD). Conversely, the NESARC-III study found a 48.2% (SE 2.51) prevalence of any current personality disorder (aOR 2.0, 95% CI 1.56–2.65) among men with current CUD [20]. Among women with current CUD, the corresponding figure was 58.6% (SE 3.17) (aOR 3.1, 95% CI 2.14–4.35). Among men, the prevalence of specific current personality disorders among those with current CUD was 24.9% (SE 2.17) (aOR 1.3, 95% CI 0.98–1.85) for schizotypal, 39.1% (SE 2.32) (aOR 2.0, 95% CI 1.46–2.67) for borderline, and 21.8% (SE 2.12) (aOR 1.5, 95% CI 1.08–2.02) for antisocial. The corresponding figures for women were 33.5% (SE 3.21) (aOR 2.0, 95% CI 1.26–3.18) for schizotypal, 49.9% (SE 3.21) (aOR 1.9, 95% CI 1.14–3.02) for borderline, and 16.1% (SE 1.95) (aOR 1.7, 95% CI 1.13–2.58) for antisocial.

The US NIS study found a 7.62% (95% CI 7.12–8.15) prevalence of any personality disorder diagnosis among the 65,767 hospitalized inpatients with CUD as their only SUD diagnosis, compared with a 1.41% (95% CI 1.33–1.48) prevalence among inpatients without a CUD diagnosis [5]. The NSW hospital study found a 9.2% prevalence of personality disorder among inpatients with CUD (OR 27.5, 95% CI 25.4–29.7) [6]. A Danish cohort study of 72,791 individuals treated for personality disorders from 1969 to 2014 (derived from several national population-based registries) found a 5.6% prevalence of comorbid CUD [27]. Among the 5,640 individuals with schizotypal disorder, 11.6% had comorbid CUD. These findings suggest a significant association between CUD and personality disorders among patients in treatment.

Treatment

A controlled clinical trial involving 136 young adults with cannabis dependence (DSM-IV criteria), 44% with comorbid antisocial personality disorder (ASPD), compared 8 weeks of manualized weekly MET/CBT with or without contingency management vs. weekly manualized individual drug counseling with or without contingency management [76]. MET/CBT was significantly more effective than drug counseling, with comparable effectiveness in the participants with ASPD (i.e., there was no significant ASPD x treatment interaction).

Adjustment Disorders

Epidemiology

We are aware of only one published study on the epidemiology of comorbid CUD and adjustment disorders. The US

NIS study found a 2.88% (95% CI 2.66–3.12) prevalence of any adjustment disorder diagnosis among the 65,767 inpatients with CUD as their only SUD diagnosis, compared with 0.64% (95% CI 0.61–0.67) among inpatients without a CUD diagnosis [5], suggesting a significant association between CUD and adjustment disorders among patients in treatment.

Treatment

We are not aware of any published clinical trials on the treatment of comorbid CUD and adjustment disorder.

Conclusions Adults with current CUD have a current prevalence of most major psychiatric disorders that is substantially greater than the prevalence of those disorders in the population without CUD, both in the community-living setting and in clinical settings. For example, prevalence rates for major psychiatric disorders in recent nationally representative epidemiological surveys in the United States and Australia range from 20 to 32% for depression, 8 to 9% for bipolar disorder, and 23 to 40% for anxiety disorders. Odds ratios for psychiatric comorbidity (compared with populations without CUD) are significantly greater than 1 in most studies, suggesting that the comorbidity is not due to chance. There is also substantial comorbidity in the reverse direction, i.e., prevalence of CUD in those with psychiatric disorders: 4–6% in depression, 15% in bipolar disorder, 5% in anxiety disorders, and 7–16% in schizophrenia. A similar pattern generally holds for comorbidity prevalence rates in clinical (treatment) populations.

Whether these statistical associations represent an actual causal relationship remains unclear. Few studies report the temporal order of onset of CUD and the psychiatric disorder; and few control for the numerous potential confounding factors, i.e., antecedent risk factors that may be common to both CUD and the psychiatric disorder, such as age, gender, socioeconomic status, history of abuse, substance use, and other psychiatric disorders. Genetic and twin studies might be informative, but these almost exclusively focus on cannabis use among those with psychiatric disorders, rather than CUD and psychiatric comorbidity.

Despite the substantial prevalence of CUD and psychiatric comorbidity and its clinical relevance for prognosis and treatment, there are relatively few clinical trials evaluating treatment. Thus, it is not surprising that no medication is approved for such an indication by the US Food and Drug Administration (FDA) or any other national regulatory authority. Single, small-scale controlled clinical trials suggest that lithium may be effective for adolescents with bipolar disorder [42] and clozapine for adults with schizophrenia [63]. There is a similar scarcity of high-quality evidence for psychosocial treatments [77]. Several small-scale, controlled clinical trials suggest that combined MET/CBT with components focused on both CUD and the psychiatric disorder can be effective in reducing cannabis use and improving psychiatric symptoms.

Current gaps in the evidence base regarding CUD and psychiatric comorbidity suggest several areas that warrant further research. These include large-scale, representative epidemiological surveys that explicitly diagnose CUD and the psychiatric comorbidity, evaluate relevant potential confounds (e.g., cannabis and other substance use), and use these data to calculate odds ratios in relation to relevant comparison populations; large-scale, long-term prospective longitudinal studies that carefully evaluate participants at baseline to exclude those with one comorbid disorder so that the incidence over time of the other disorder can be accurately assessed; and genetic and twin studies that focus on diagnosed disorders in addition to substance use. There is also an urgent need for high-quality controlled clinical trials of both pharmacological and psychosocial treatments (and their combination) that involve participants with specifically diagnosed CUD and comorbid psychiatric disorders. Promising medications to study include lithium for comorbid bipolar disorder and clozapine (and possibly quetiapine) for comorbid schizophrenia.

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