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Review article

# Comorbid Cannabis Use Disorder with Major Depression and Generalized Anxiety Disorder: A Systematic Review with Meta-analysis of Nationally Representative Epidemiological Surveys

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ABSTRACT

*Background:* Studies have shown a high degree of comorbidity between cannabis use disorder (CUD) and other mental illnesses. However, there is a paucity of research on the comorbidity between CUD with major depression (MD) and generalized anxiety disorder (GAD). This systematic review with meta-analysis aimed to assess the prevalence and strength of association between co-morbid CUD with MD and GAD.

*Methods:* An extensive search of Medline, CINAHL, PsycINFO, EMBASE, and grey literature were conducted to cover articles published between January 1st, 1980, and July 31st, 2020. Inclusion criteria were publications in English Language, original research, nationally representative samples, and non-clinical randomly selected adult populations. A systematic review and meta-analysis for the prevalence and ORs for comorbid CUD with MD or GAD were done.

*Results:* A total of 67 articles were identified by the electronic searches. A full-text review yielded 8 publications on nationally representative epidemiological surveys. 12-month and lifetime comorbidity estimates were extracted and used for the meta-analysis. CUD was strongly associated with MDE (OR 3.22; 2.31 - 4.49) and with GAD (OR 2.99; 2.14 - 4.16).

*Limitations:* Limitations of this study include the heterogeneity observed due to the combination of studies from different geographic regions with different modifications of diagnostic criteria and varied response rates. This was addressed with a random-effects model.

*Conclusion:* This review confirms the evidence of high prevalence and a 3-fold comorbid association between CUD with MD and CUD with GAD. Implementation of evidence-based policy interventions with effective, integrated management of comorbid CUDs with psychiatric disorders may contribute to positive patient outcomes.

## 1. Introduction

Globally, cannabis is the most consumed illicit substance (United Nations Office on Drugs and Crime (UNODC), 2018; Degenhardt and Hall, 2012) and in 2009, it was estimated that between 125 and 203 million individuals use cannabis at least once (Degenhardt and Hall, 2012). In USA, 1 in 5 young adults (19.6 percent) aged 18 to 25 used marijuana in the past month in 2014 (Center for Behavioral Health Statistics and Quality, 2015) while approximately 50% of Canadians aged 15 or older reported lifetime cannabis use in 2017 (Health Canada, 2019). In 2010, cannabis use among those 14 years and older in Australia increased from 9.1% in 2007 to 10.3% (Australian Institute of Health and Welfare, 2011). In Europe, nearly 20% of young adults (15-24 age group) reported having used cannabis in 2018 (European Monitoring Centre for Drugs and Drug Addiction, 2019), and approximately 40% of young adults in Germany, Netherlands, and Czech Republic have a lifetime use of cannabis in 2018 (European Monitoring Centre for Drugs and Drug Addiction, 2020). Although cannabis can be used for a range of medical reasons (Whiting et al., 2015), its regular or chronic use is associated with numerous harms to users (Volkow et al., 2014; Degenhardt and Hall, 2012).

Potential adverse long-term outcomes from cannabis use include risk

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of addiction (Lopez-Quintero et al., 2011), increased risk of the use of other illicit drugs (Hall and Degenhardt, 2007) and significant IQ decline (Meier et al., 2012). Evidence suggests that persistent cannabis use often leads to cannabis abuse and/or dependence (George and Vaccarino, 2015; Volkow et al., 2014; Silins et al., 2014; Pearson et al., 2013). These two case definitions have been included in the modified DSM-5 diagnostic criteria for cannabis use disorder (CUD) (American Psychiatric Association, 2013; Hasin et al., 2013). CUD is associated with a high risk of other substance use disorders (Volkow et al., 2014), low quality of life (Lev-Ran et al., 2012), low educational achievement (Lynskey and Hall, 2000), cognitive decline (Renard et al., 2013), impaired driving capability (Hartman and Huestis, 2013; Hartman et al., 2015), and psychiatric symptoms (Davis et al., 2013; Di Forti et al., 2015).

Previous studies have shown a high degree of comorbidity between drug use disorders and mental illness (Conway et al., 2006) and CUD with other substance use disorders (Khan et al., 2013). However, there is a paucity of research on the comorbidity of CUD with other psychiatric disorders (Agnosti et al., 2002), particularly, comorbidity with Major Depression (MD) and Generalized Anxiety Disorder (GAD) has not been well-established for nationally representative mental health surveys. A better understanding of the co-occurrence of CUD with these two conditions might provide a platform for effective clinical management of patients (Wilson and Cadet, 2009).

This systematic review with meta-analysis is intended to expand current knowledge by assessing the prevalence and strength of associations between comorbid CUD with GAD and MD in nationally representative samples. Comorbidity has been shown to be a significant predictor of treatment seeking (Wu et al., 1999), therefore, nationally representative studies where chosen to avoid including studies based on treatment samples that may overestimate the comorbid associations (Berkson, 1946). Due to the more severe and protracted mental health disorders that characterize comorbidity, the resultant increased help-seeking behavior bias treatment samples (Berkson, 1946; Regier et al., 1990; Rounsaville et al., 1987). In addition, to avoid population dynamics such as rural versus urban differences and the influence on comorbid treatment access and estimates, our focus was on national surveys only. General population-based studies provide more robust and generalizable estimates of the comorbidity distribution of CUD and mental health disorders.

Our focus on CUD can be attributed to 1) the growing popularity of legalizing and regulating recreational cannabis, and 2) how its medical uses fit into the equation (Canadian Centre on Substance Abuse, 2017; United Nations Office on Drugs and Crime, 2016). For instance, in Canada, cannabis legalization took place on the 17$^{th}$ of October 2018, and previous studies have been inconsistent on the adverse health effects CUD (Canadian Centre on Substance Abuse, 2017). Examination of fatally injured drivers in Canada found that 18.9% tested positive for cannabis use in 2014 (Brown et al., 2017) whereas a recent Canadian study found no association between vehicle accidents and cannabis use (Brubacher et al., 2019). In Colorado, USA, a 32% and 92% increase in cannabis-related traffic fatalities was recorded after legalizing cannabis use at one year and four year, respectively (Lin et al., 2015; Salomonsen-Sautel et al., 2014). These findings could be attributed to the short-term intoxicating and impairing effects of cannabis on psychomotor skills required for safe driving, deficits in attention span and slow reaction time of drivers (Lin et al., 2015; Asbridge et al., 2012; Salomonsen-Sautel et al., 2014).

This systematic review's pooled effect estimates would help to clarify the nature and extent of the relationship between cannabis use disorders (CUDs) i.e. cannabis abuse, cannabis dependence or cannabis use disorder (CUD) with GAD and MD.

## 2. Objectives

This systematic review with meta-analysis is aimed to assess the strength of association between comorbid cannabis use disorder (CUD) – cannabis abuse, cannabis dependence, or CUD with MDE and comorbid CUDs with GAD in nationally representative population-based surveys.

## 3. Methods

The methods were based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Liberati et al., 2009; Moher et al., 2009).

### 3.1. Data sources and search strategy

A computerized search of the following bibliographic databases: MEDLINE, CINAHL, PsycINFO and EMBASE was conducted using the following search terms: (co-morbid* or comorbid* or co-occur*) OR diagnosis or dual diagnosis(psychiatry), AND (cannabis* or marijuana* or drug* or substance* or CUD) OR (mental health or mental illness or depress* or mood disorder or anxiety or GAD) AND (epidemiology or prevalence or incidence or occurrence), for population surveys of humans in English, published online between January 1$^{st}$ 1980 and July 31$^{st}$ 2020. Further search was done for related articles of selected authors (e.g. de Graaf, Grant, Kessler, Merikangas, Reiger, Conway and Swendson), the reference list of included studies and grey literature for dissertations, conference abstracts, formally unpublished journal articles and books were made. Inclusion criteria were publications of original research in English Language, non-clinical, nationally representative, and randomly selected adult populations. Exclusion criteria were studies done on treatment/ clinical/ patient samples, restricted geographic area (e.g. city), a defined cohort population of a country (e.g. students, veterans), children and adolescent.

### 3.2. Selection criteria

*Inclusion criteria:* 1) Articles were chosen if they were original research on adults that were randomly selected into nationally representative surveys, 2) All included studies had diagnoses for CUD, major depression and GAD based on structured diagnostic instruments. *Exclusion criteria: 1)* Children and adolescent studies were excluded because interviews on them are usually complicated with consent and proxy issues, 2) Studies on subpopulations such as specific cities (e.g. Ontario (Offord et al., 1996), Munich (Wittchen et al., 1992), 3) specific age group (e.g. middle-aged), 4) gender-specific or other specific demographics (e.g. veterans, nurses, students), race (Merikangas et al., 1998), 5) other comorbidities (e.g. diabetes), institutionalized, and homelessness were excluded as they were not nationally representative. The diagnostic criteria for assessing CUD, major depression and GAD were also used to screen studies. In all included studies diagnoses were based on structured diagnostic instruments.

Selected articles were reviewed and assessed for risk of bias using the tool developed by Hoy et al. (2012) by two independent reviewers (TOF and VNO). The first, second and third rounds of exclusions were based on the articles' titles, abstracts and full texts respectively. A full text review was done if there were any disagreements or uncertainties at the first (title) and second (abstract) rounds of the review. A third rater (CD) resolved any disagreements with the full text review.

### 3.3. Data abstraction

Semi-structured forms were used by the two raters (TOF and VNO) to independently abstract the study characteristics such as, the name of study, name of survey, authors, setting (country), year the survey was conducted, year of publication, journal name, sample size, age range of target population, diagnostic criteria used to assess substance use disorders (SUD) and psychiatric disorders, type of CUD (i.e. CUD, cannabis abuse, cannabis dependence) and psychiatric disorders (major depression and GAD).

The meta-analysis data abstraction included the comorbidity prevalence, odds ratios (ORs) and 95% confidence intervals of major depression, GAD, and cannabis use disorders.

### 3.4. Meta-analysis

STATA version 14 was used to estimate the pooled ORs of selected articles for Cannabis use disorders (CUDs) with MD and CUDs with GAD.

In these analyses, cannabis use disorders (CUDs) consisted of the spectrum of the disorder that occur with cannabis use, i.e. cannabis use disorder (CUD), cannabis abuse and cannabis dependence. All diagnoses were derived using structured diagnostic instruments in the primary studies.

Heterogeneity with DerSimonian and Laird $I^2$ Statistic was used to determine the degree of inconsistency across studies' results that is secondary to heterogeneity rather than chance (Higgins et al., 2003), since the estimates would likely vary between populations of different nationalities and characteristics. A significant percentage of total variation across studies led to the choice of using random effects models as opposed to fixed effects models to account for the heterogeneity. To avoid duplication, articles reporting odds ratios from the same survey were identified and one selected based on quality, estimates reported (lifetime chosen over 12-months) and date of publication (most recent chosen). Publication bias was accounted for with Egger's test and impact of study quality with meta-regression. Sensitivity analysis was done to see the impact of individual studies on the overall estimate. All the studies included in the review were judged to be of high quality.

## 4. Results

### 4.1. Search findings

A total of 1133 titles were identified (Fig. 1) after removal of duplicates. 795 articles were judged as not relevant by title by the two

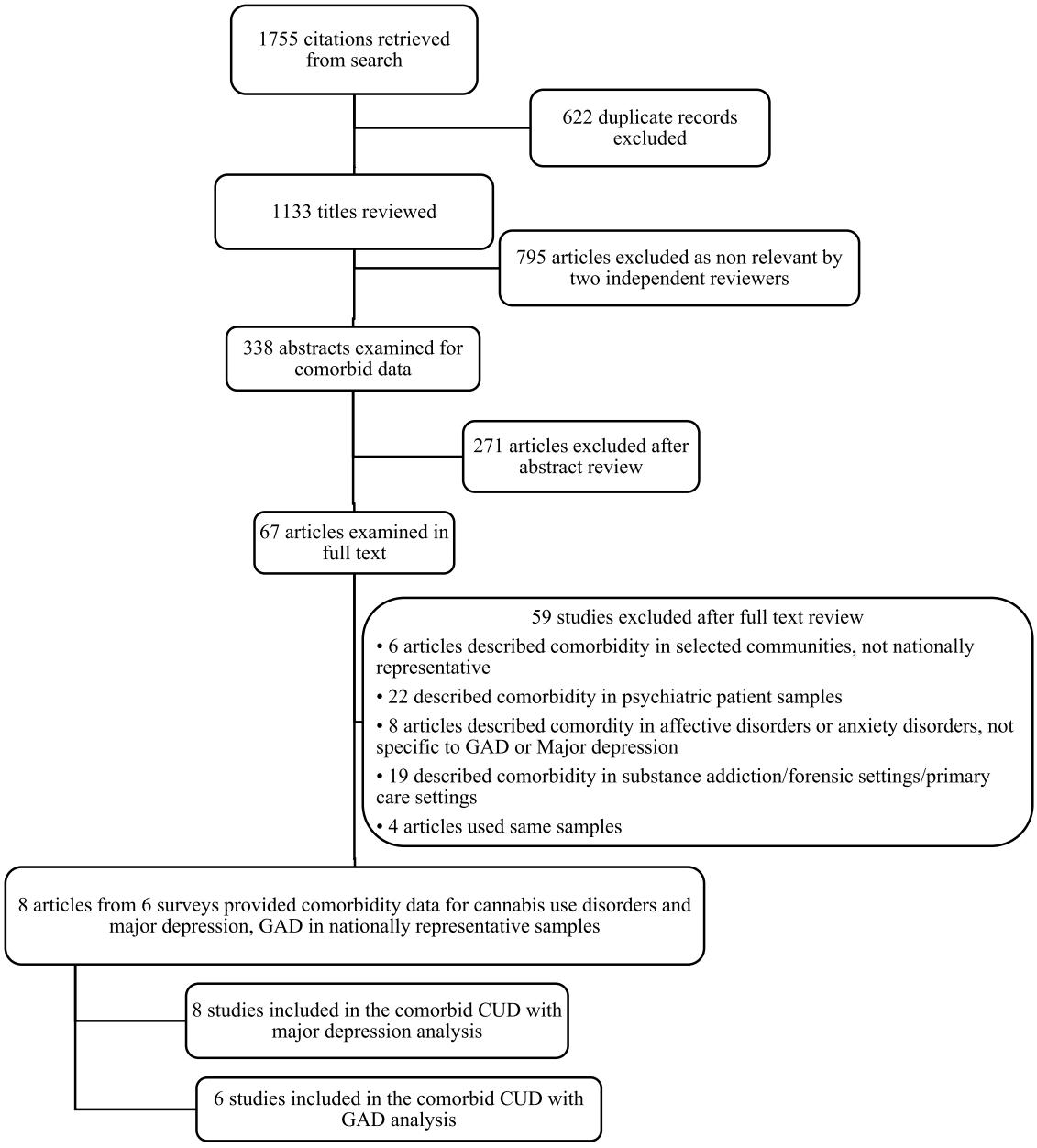



**Fig. 1.** PRISMA flow diagram of search strategy
CUD, cannabis use disorder; GAD, generalized anxiety disorder.

independent reviewers (VNO and TOF). Abstract review of 338 articles for comorbid associations was done and 271 articles were excluded. After a full text review of the remaining 67 articles, 8 articles from 6 epidemiological surveys were identified as describing comorbid prevalence and associations in nationally representative samples.

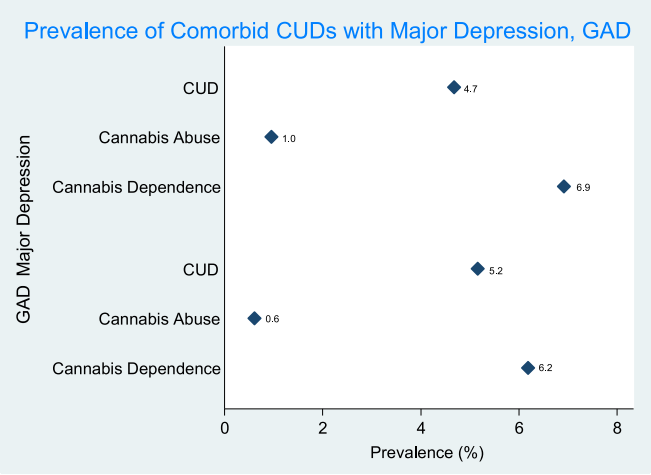
### 4.2. Study characteristics

The 8 articles included in this review have been summarized in Table 1 showing the settings, sample sizes, characteristics of the respondents and diagnostic instruments. Sample sizes ranged from 5,877 to 43,093 with a total sample size of 176,976 for all 6 surveys included in the analysis. Surveys included were largely from the USA and Australia. Some national surveys that were repeated at different time points with different respondents such as the National Epidemiological Survey on Alcohol and Related Conditions - NSERC wave I (Study ID 3,4) and III (study ID 5) were included as different studies while the one that was based on the same respondents (NSERC wave II) from a previous survey (NSERC wave I) was excluded. Studies that assessed different dimensions of the substance use disorder independently such as cannabis abuse or cannabis dependence on the same sample (Grant, 1995, National Longitudinal Alcohol Epidemiology Survey, NLAES) were included as separate studies.

A modified assessment scale using the Newcastle-Ottawa Scale (NOS) and the tool developed for prevalence studies by Hoy et al (Hoy et al., 2012; Wells et al., 2012) was used to assess the quality of the studies and risk for bias (Appendix 3). The assessment of study quality was based on the external validity (sampling frame a true representation of the target population, random selection of participants, likelihood of non-response minimal, representativeness of the national population) and internal validity (assessment of exposure and outcome, data collected directly from the subjects not proxy, acceptable case definition used in the study, the same mode of data collection for all subjects, appropriate numerator(s) and denominator(s) for the parameter of interest, appropriate control of confounding) of the studies (Hoy et al., 2012; Wells et al., 2012). Although two studies (from the National Comorbidity Survey, NCS) reported crude estimates only, all studies included in the analysis were of high quality and judged to have a low risk of bias by the raters.

### 4.3. Prevalence

The population prevalence of major depression co-occurring with cannabis dependence (6.9%) was found to be more than with CUD (4.7%) while its co-occurrence with cannabis abuse was 1.0% (Fig. 2). Similarly, Cannabis dependence comorbid with GAD (6.2%) was more prevalent than CUD with GAD (5.2%) and cannabis abuse with GAD




CUD, Cannabis use disorders; GAD, Generalized Anxiety Disorder

**Fig. 2.** Prevalence of comorbid substance use disorders with major depression CUD, Cannabis use disorders; GAD, Generalized Anxiety Disorder.

**Table 1**
Summary of study characteristics of reviewed studies.

| Study ID | Survey name | Survey year | Setting | First author | Sample size | Age range (year) | Psychiatric disorders | SUDs | Diagnostic criteria | Risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | National Comorbidity Survey (NCS) | 1990-1992 | United States | (Agnosti et al., 2002) | 5,877 | 15-54years | Major Depression, GAD | Cannabis Dependence | DSM-III-R | Low |
| 2 | | | | (Chen et al., 2002) | 5877 | 15-54years | Major Depression | Cannabis Dependence | DSM-III-R | Low |
| 3 | National Epidemiologic Survey on Alcohol and Related Conditions (NSERC) | 2001-2002 | United States | (Conway et al., 2006) | 43,093 | 18years and older | Major depression, GAD | CUD, abuse, dependence | AUDADIS-IV derived from DSM-IV | Low |
| 4 | | | | (Stinson et al., 2006) | 43,093 | 18years and older | Major depression, GAD | CUD | AUDADIS-IV derived from DSM-IV | Low |
| 5 | National Epidemiological Survey on Alcohol and Related Conditions (NESARC) III | 2012-2013 | United States | (Hasin et al., 2016) | 36, 309 | 18years and older | Major depression, GAD | CUD | AUDADIS-5 derived from DSM-5 criteria | Low |
| 6 | National Household Survey on Drug Abuse (NHSDA) | 1994, 1995, 1996 | United States | (Kandel et al., 2001) | 39,994 | 12years and older | Major depression | Cannabis dependence | DSM-IV | Low |
| 7 | National Longitudinal Alcohol Epidemiology Survey (NLAES) | 1992 | United States | (Grant, 1995) | 42,862 | 18years and older | Major depression | CUD, abuse, dependence | AUDADIS-IV derived from DSM-IV | Low |
| 8 | National Survey of Mental Health and Well Being (NSMH&WB) | 2007 | Australia | (Teesson et al., 2012) | 8841 | 16-85yeasr | Major depressive ds, GAD | CUD | WMH-CIDI derived from DSM-IV | Low |

SUD, Substance use disorder; CUD, Cannabis use disorders; DSM, Diagnostic Statistical Manual of Mental Disorders; AUDADIS-IV, Alcohol Use Disorder and Associated Disabilities Interview Schedule – DSM-IV version; AUDADIS-5, The Alcohol Use Disorder and Associated Disabilities Interview Schedule-5; WMH-CIDI, World Mental Health Composite International Diagnostic Interview

(0.6%).

### 4.4. Meta-analysis

The overall meta-analysis pooled OR for CUDs (i.e. cannabis abuse, cannabis dependence, CUD) with major depression (Fig. 3) was 3.22 (95%CI 2.31 - 4.49) on 8 studies. The pooled OR for cannabis dependence with depression sub-analysis was 4.83 (95%CI 3.05 – 7.63) while the CUD with depression and cannabis abuse with depression sub-analyses were 2.60 (95%CI 2.37 – 2.85) and 2.37 (95%CI 1.38 – 4.07) respectively. In other words, individuals with some form of CUD were about 2 to 5 times more likely to have comorbid major depression. All the studies in the analyses except Teesson et al (2012) (based on the 2007 Australian National Survey of Mental Health and WellBeing) found a significant risk of comorbid major depression with either cannabis abuse, dependence, or CUD.

Fig. 4 is the meta-analysis of pooled ORs for CUDs (i.e. cannabis abuse, cannabis dependence, and CUD) with generalized anxiety disorder. Overall, the comorbid risk of GAD in cannabis use disorders is about 3 times greater (OR 2.99; 95%CI 2.14 - 4.16). In cannabis dependence, the comorbid risk of GAD is more than 4 times greater (OR 4.35; 95%CI 1.73 - 10.91) while the risk is about 2 to 3 times for cannabis abuse (OR 1.80; 95%CI 1.40 – 2.31) and CUD (OR 2.93; 95%CI 2.52 - 3.42) respectively.

The DerSimonian and Laird $I^2$ test for heterogeneity was significant ($p<0.0001$) and a random effects analysis was chosen to account for the heterogeneity in the included studies. There was no evidence of publication bias with Egger's test on all analyses.

## 5. Discussion

This systematic review with meta-analysis of nationally representative samples showed a three-fold increase in the risk of comorbid CUD with GAD (pooled OR 2.99) and comorbid CUD with MD (pooled OR 3.22). Thus, demonstrating that the comorbidity of CUD with GAD and CUD with MD is pervasive in the general population.

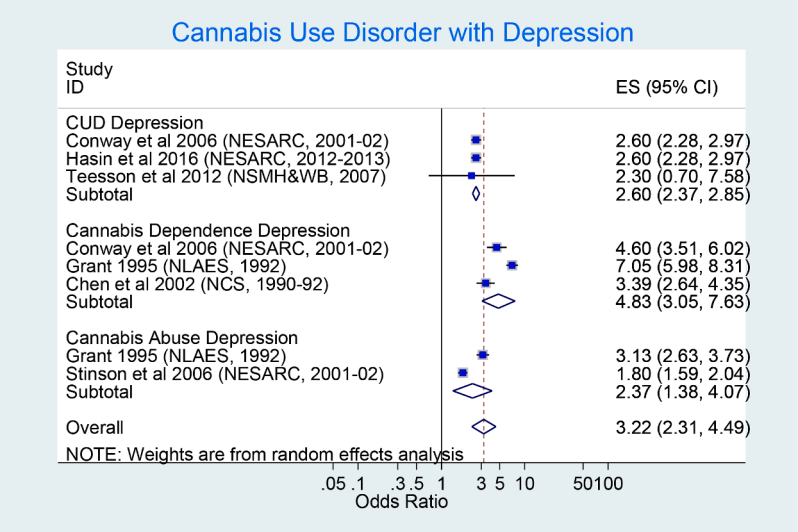
We also found a high prevalence between CUD with GAD (5.2%) and CUD with MD (4.7%). This is consistent with the study by Conway et al (2006) that found CUD as the most prevalent substance use disorder with a prevalence of 9.1% for GAD, and a significantly higher rate of 31.9% for MD among those who had cannabis use disorder (Conway et al., 2006). In addition, this is consistent with the study by Agnosti et al. (2002), who reported a high prevalence for lifetime comorbidity of Cannabis Dependence with MD (32.7%) and GAD (12.1%) (Agnosti et al., 2002).

### 5.1. Cannabis use disorders with major depression

The evidence reported suggested that MD was strongly associated with CUD, and this association was stronger with cannabis dependence (pooled OR 4.83). A closer inspection of the forest plot showed one of eight studies did not find a significant risk of comorbid MD with CUD (Teesson et al., 2012). This meta-analysis, confirms the findings from several studies that cannabis, particularly, heavy use increases the risk of comorbid major depression (Arseneault et al., 2002; Chen et al., 2002; Cheung et al., 2010; van Laar et al., 2007; Degenhardt et al., 2003; Fergusson et al., 2002; Lynskey et al., 2004; Hayatbakhsh et al., 2007; Marmorstein and Iacono, 2011; Bovasso, 2001).

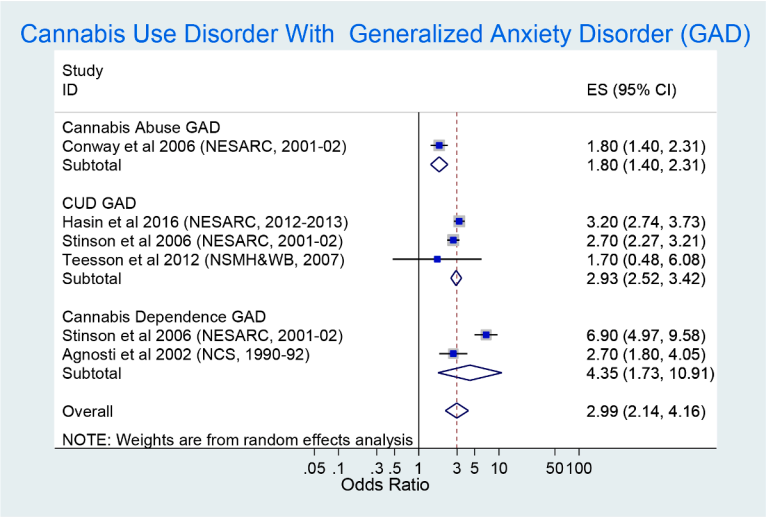
Given that these associations are not necessarily causal, several mechanisms leading to the occurrence of comorbid CUD and MD have been proposed. First, biological effects where cannabis causes multiple effects in the brain chemistry, thus increasing the likelihood of depression (Degenhardt et al., 2003; Hayatbakhsh et al., 2007; van Laar et al., 2007; Patton et al., 2002; Dean et al., 2001). It is biologically plausible that long-term cannabinoid consumption may alter the responsiveness of the serotonin system in ways consistent with depression (Hill et al., 2006; Tsou et al., 1999; Bhagwager et al., 2004; Drevets et al., 1999; Sargeant et al., 1990). Another mechanism is shared vulnerability where common genetic and/or environmental vulnerabilities predispose some people to have impaired psychosocial adjustment from which mental health problems including substance use disorders could arise and co-occur (Lynskey et al., 2004; Degenhardt et al., 2003). In addition, the adverse psychological consequences of CUD such as educational under-achievement, unemployment, and crime can exacerbate this association (Marmorstein and Iacono, 2011; Lev-Ran et al., 2014; Degenhardt et al., 2003).

In contrast to the above hypotheses that sees major depression resulting from the cannabis use disorder, the self-medication theory postulates that mental health disorders actually lead to substance use disorder due to the misuse of substances to alleviate mental health symptoms (Canadian Centre on Substance Abuse, 2009; Khantzian, 1985). For example, individuals with depression or anxiety will




ES – estimate (OR); CUD - Cannabis use disorder

**Fig. 3.** Comorbid cannabis use disorders with major depression
ES – estimate (OR); CUD - Cannabis use disorder.




ES – estimate (OR); CUD - Cannabis use disorder

**Fig. 4.** Comorbid cannabis use disorders with Generalized Anxiety Disorders (GAD)
ES – estimate (OR); CUD - Cannabis use disorder.

self-medicate with a substance such as cannabis for the calming or euphoric effect. However, irrespective of the pathway that led to the comorbid state, it does appear that once an individual has developed both, a vicious cycle may be at play where each disorder maintains or exacerbates the other (Canadian Centre on Substance Abuse, 2009).

### 5.2. Cannabis use disorders with generalized anxiety disorder

CUD is highly associated with GAD and this was confirmed in our meta-analysis pooled OR of 2.99. Closer inspection of the forest plots shows all estimates reported significant associations except the study by Teeson et al (2012) using the 2007 Australian National Survey of Mental Health and WellBeing survey. Our pooled estimate confirmed findings from epidemiological surveys of increases in risk of comorbid CUD with GAD ((Agnosti et al., 2002; Chen et al., 2002; Conway et al., 2006; Hasin et al., 2016; Stinson et al., 2006).

This finding may be attributed to the bidirectional effect of cannabis on anxiety (Leweke and Koethe, 2008) where chronic CUD could lead to development of anxiety symptoms and individuals with anxiety could experience some relief from their symptoms with cannabis use. These biphasic relationships could be as a result of dose-dependent interaction between delta-9-tetrahydrocannabinol (a potent cannabis compound), neurotransmitter systems and endocannabinoid dysregulations (Crippa et al., 2009; Leweke and Koethe, 2008). In addition, early cannabis use may affect cognitive functioning and brain cells maturation among adolescents (Solowij and Pesa, 2010) thereby predisposing the users to subsequent development of anxiety (Wilson and Cadet, 2009).

### 5.3. Strengths and limitations

Consistently, strong associations in nationally representative sample data between CUD and MD; and CUD and GAD are evident in this analysis. The methods used in the primary research studied were relatively consistent, with face-to-face interviews from random samples of general populations at the national level, and the structured diagnostic methods to derive the diagnosis of MD, GAD, and cannabis use disorders. Some of the limitations of this study were the interview-based diagnoses which did not allow for the elimination of differential diagnoses, possibly inflating prevalence, and associations in the original studies; and the inclusion of publications in English Language only, possibly introducing publication bias. It is possible that there might be double counting of controls in the meta-analysis since some studies that assessed the different comorbidities of CUD in the sample population were included. However, this is negligible as the sample sizes are large (Senn, 2009). The heterogeneity observed in this study was probably due to the combination of studies across different geographic regions and cultures with varied response rates, different modifications of different versions of the Diagnostic Statistical Manual (DSM) or International Classification of Diseases (ICD) diagnostic criteria, the varying depth of interviews, and adjustments of prevalence and associations of the comorbidity.

## 6. Conclusions and public health implication

In summary, our study findings provide further evidence on the strength of comorbid association of CUD with MD and CUD with GAD in the general population. The rates of comorbid MD and GAD is three times higher among those with CUD. This evidence should help guide clinical management of patients with comorbid CUD and mental health illness, which has often been associated with inadequate treatment, poor prognosis, and high levels of health service utilization (Hasin et al., 2016; Kessler, 2004). A thorough understanding of the way and reasons CUD co-occur with GAD and MD may provide effective prevention and treatment guidelines that focus on integrated shared-care approaches and/or psychosocial treatment in parallel systems (Horsfall et al., 2009; Mills et al., 2012; Tiet and Mausbach, 2007), as well as mitigate barriers in clinical management of patients with a comorbid diagnosis (Mills et al., 2012).

Given the increasing prominence of cannabis use along with ongoing changes in cannabis legalization in legalization in many countries (Statistics Canada, 2019; Hawley et al., 2020), it is imperative to mitigate the serious health-related harms of CUD, such as increased risk of comorbid anxiety or depression (Patton et al., 2002); high risk of myocardial infarction, stroke, and transient ischemic attacks (Thomas et al., 2014); increased ER visits and fatal car accident (Brady and Li, 2014)); and crime (Schauer et al., 2016). There is a great need for stronger evidence-based policy interventions that include, public health education about potential harms and responsible use (Murray et al., 2007); increased clinicians training about treatment prognosis; more health care funding due to increase service utilization of comorbidity; and reduce social stigmatization of individuals who seek treatment.

## Author Contributions

Conceived and designed the study: VNO, TOF.
Systematic review and article rating – VNO, TOF, CD
Analyzed the data: VNO
Contributed materials/analysis tools: VNO, TOF, CD.
Wrote the paper: VNO, TOF, CD.

## Declaration of Competing Interest

None.

## Funding

None.

## Acknowledgements

None.

## Appendix 1 Search Strategy

*MEDLINE*

(((((co-morbid* or comorbid* or co-occur* or diagnosis or dual diagnosis psychiatry,) and cannabis* or marijuana* or drug* or substance* or SUD or mental health or mental illness or bipolar or depress* or mood disorder or GAD or anxiety) and epidemiology) or prevalence or incidence or occurrence).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word]

Limits - Full Text; Abstract Available; Published Date: 19800101-20200731; English Language; Research Article; Human

*CINAHL*

1 (co-morbid* or comorbid* or co-occur*) OR diagnosis or dual diagnosis(psychiatry), AND (cannabis* or marijuana* or drug* or substance* or SUD) OR (mental health or mental illness or bipolar or depress* or mood disorder) AND (epidemiology or prevalence or incidence or occurrence)

**Limiters** - Full Text; Abstract Available; Published Date: 19800101-20200731; English Language; Research Article; Exclude MEDLINE records; Human

2 **Search modes** - Find all my search terms

*EMBASE*

1 ((((co-morbid* or comorbid* or co-occur* or diagnosis or dual diagnosis psychiatry,) and cannabis* or marijuana* or drug* or substance* or SUD or mental health or mental illness or bipolar or depress* or mood disorder or GAD or anxiety) and epidemiology) or prevalence or incidence or occurrence).mp. [mp=title, abstract, heading word, original title, keyword, floating subheading word]
2 limit 1 to (full text and abstracts and human and Cochrane library and English language and yr="1980 - 2020")

*PsychINFO*

1 (((((co-morbid* or comorbid* or co-occur* or diagnosis or dual diagnosis psychiatry,) and alcohol*) or cannabis* or marijuana* or drug* or substance* or SUD or mental health or mental illness or bipolar or depress* or mood disorder or anxiety or GAD) and epidemiology) or prevalence or incidence or occurrence).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
2 limit 1 to (human and English language and yr="1980 - 2020"
3 limit 2 to (full text and human and English language and abstracts and yr="1980 - 2020")

## Appendix 2 Data references

Agnosti et al. (2002). Rates of Psychiatric Comorbidity Among U.S. residents with Lifetime Cannabis Dependence. The American Journal of Drug and Alcohol Abuse, 28(4), 643-652.

Chen et al. (2002). Marijuana use and the risk of major depressive episode: epidemiological evidence from the United States National Comorbidity Survey. Soc. Psychol. Psychitric Epidemiology, 37, 199-206.

Conway et al. (2006). Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and related conditions. J. Clin. Psychiatry, 67, 247-257.

Grant, B. (1995). Comorbidity between DSM-IV drug use disorders and major depression. J. Subst. Abuse, 7, 481-497.

Hasin et al. (2016). Prevalence and Correlates of DSM-5 Cannabis Use Disorder, 2012-2013: Findings from the National Epidemiologic Survey on Alcohol and Related Conditions-III. Am J Psychiatry, 173, 588-599.

Kandel et al. (2001). Comorbidity between patterns of substance use dependence and psychiatric syndromes. Drug Alcohol Depend., 64, 233-241.

Stinson et al. (2006). Cannabis use disorders in the USA: prevalence, correlates and comorbidity. Psychological Medicine, 36, 1447-1460.

Teesson et al. (2012). Prevalence, correlates and comorbidity of DSM-IV cannabis use and cannabis use disorders in Australia. Australian & New Zealand Journal of Psychiatry, 46(12), 1182-1192.

## Appendix 3. Assessment of study quality

External validity

1 Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex? • 1 -Yes (LOW RISK): The study's target population was a close representation of the national population. • 0 - No (HIGH RISK): The study's target population was clearly NOT representative of the national population.
2 Was the sampling frame a true or close representation of the target population? • 1-Yes (LOW RISK): The sampling frame was a true or close representation of the target population. • 0 - No (HIGH RISK): The sampling frame was NOT a true or close representation of the target population.
3 Was some form of random selection used to select the sample, OR, was a census undertaken? • 1-Yes (LOW RISK): A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling). •0 - No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.
4 Was the likelihood of non-response bias minimal? • 1-Yes (LOW RISK): The response rate for the study was >/=75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non-responders • 0 - No (HIGH RISK): The response rate was < 75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders

Internal validity

| First Author | National Repres-entation[1] | Close representation of target population[2] | Random selection[3] | Non-response bias minimal[4] | Data collection from subjects[5] | Case definition[6] | Assessment of exposure[7] | Assessment of outcome[8] | Data collection method the same[9] | Confounding control[10] | TOTAL | Risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Agnosti et al., 2002 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 9 | Low, crude estimates reported |
| Chen, 2002 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 9 | Low, crude estimates reported |
| Conway et al., 2006 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 10 | Low |
| Stinson et al., 2006 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 10 | Low |
| Hasin et al., 2016 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 10 | Low |
| Kandel et al., 2001 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 10 | Low |
| Grant, 1995 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 10 | Low |
| Teesson et al., 2012 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 10 | Low |

1 Were data collected directly from the subjects (as opposed to a proxy)? • Yes (LOW RISK): All data were collected directly from the subjects. • No (HIGH RISK): In some instances, data were collected from a proxy.

2 Was an acceptable case definition used in the study? • 1 - Yes (LOW RISK): An acceptable case definition was used. • 0 - No (HIGH RISK): An acceptable case definition was NOT used.

3 Assessment of exposure: use of structured clinical interview derived from structured diagnostic criteria for substance use disorders (DSM-III/IV/V, CIDI)? • 1 - Yes (LOW RISK) • 0 - No (HIGH RISK): questions from published health surveys/screening instruments, own system, symptoms described, no system, not specified, or self-reported

4 Assessment of outcome: use of structured clinical interview derived from structured diagnostic criteria for major depression (DSM-III/IV/V, CIDI)? • 1 - Yes (LOW RISK) • 0 - No (HIGH RISK): questions from published health surveys/screening instruments, own system, symptoms described, no system, not specified, or self-reported

5 Was the same mode of data collection used for all subjects? • 1 - Yes (LOW RISK): The same mode of data collection was used for all subjects. • 0 - No (HIGH RISK): The same mode of data collection was NOT used for all subjects

6 Appropriate methods to control confounding: • 1 - Yes (LOW RISK): multivariable adjusted OR including SES, education in models. • 0 - No (HIGH RISK): univariate analysis or controls for age/sex only.

CIDI - Composite International Diagnostic Interview; DSM- Diagnostic Statistical Manual

## References


Agnosti, V., Nunes, E., Levin, F., 2002. Rates of Psychiatric Comorbidity Among U.S. residents with Lifetime Cannabis Dependence. Am. J. Drug Alcohol Abuse 28 (4), 643–652.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders (Fifth ed.). American Psychaitric Publishing, Arlington, VA.

Arseneault, L., et al., 2002. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. Br. Med. J. 325, 1212–1213.

Asbridge, M., Hayden, J.A., Cartwright, J.L., 2012. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. BMJ 344, e536.

Australian Institute of Health and Welfare, 2011. 2010 National Drug Strategy Household Survey Report Drug Statistics Series No. 25.

Berkson, J., 1946. Limitations of the application of the 4-fold table analyses to hospital data. Biometrics 2, 47–53.

Bhagwager, Z., et al., 2004. Persistent reduction in brain serotonin1A receptor binding in recovered depressed men measured by positron emission tomography with [11C] WAY-100635. Mol. Psychiatry (9), 386–392.

Bovasso, G., 2001. Cannabis abuse as a risk factor for depressive symptoms. Am. J. Psychiatry 158, 2033–2037.

Brady, J.E., Li, G., 2014. Trends in alcohol and other drugs detected in fatally injured drivers in the United States, 1999–2010. Am. J. Epidemiol. 179, 692–699.

Brown, S., Vanlaar, W., Robertson, R., 2017. The Alcohol and Drug-Crash Problem in Canada. 2014 Report. CCMTA Road Safety Research Report Series. Canadian Council of Motor Transport Administrators, Ottawa.

Brubacher, J., et al., 2019. Cannabis use as a risk factor for causing motor vehicle crashes: a prospective study. Addiction 114 (9), 1616–1626.

Canadian Centre on Substance Abuse, 2009. Substance Abuse in Canada: concurrent Disorders. Canadian Centre on Substance Abuse, Ottawa, ON.

Canadian Centre on Substance Abuse, 2017. Canadian Drug Summary: Cannabis. Canadian Centre on Substance Use and Addiction (CCSA), Ottawa.

Center for Behavioral Health Statistics and Quality, 2015. Behavioral Health Trends in the United States: Results from the 2014 National Survey on Drug Use and Health, NSDUH Series H-50. HHS Publication No. SMA 15-4927.

Chen, C., Wagner, F., Anthony, J., 2002. Marijuana use and the risk of major depressive episode: epidemiological evidence from the United States National Comorbidity Survey. Soc. Psychol. Psychitric Epidemiol. 37, 199–206.

Cheung, J.T.W., et al., 2010. Anxiety and mood disorders and cannabis use. Am. J. Drug Acohol Abuse 36, 118–122.

Conway, K.P., Compton, W., Stinson, F.S., Grant, B.F., 2006. Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on alcohol and related conditions. J. Clin. Psychiatry 67, 247–257.

Crippa, J.A., et al., 2009. Cannabis and anxiety: a critical review of the evidence. Hum. Psychopharmacol. 24 (7), 515–523.

Davis, G.P., et al., 2013. Association between cannabis use, psychosis, and schizotypal personality disorder: findings from the National Epidemiologic Survey on alcohol and related conditions. Schizophr. Res. 151, 197–202.

Dean, B., et al., 2001. Studies on [3H]CP-55940 binding in the human central nervous system: regional specific changes in density of cannabinoid-1-receptors associated with schizophrenia and cannbis use. Neuroscience 103, 9–15.

Degenhardt, L., Hall, W., 2012. Extent of illicit drug use and dependence, and their contribution to the global burden of disease. Lancet 379 (9810), 55–70.

Degenhardt, L., Hall, W., Lynskey, M., 2003. Exploring the association between cannabis use and depression. Addiction 98, 1493–1504.

Di Forti, M., et al., 2015. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. Lancet Psychiatry 2, 233–238.

Drevets, W., et al., 1999. PET imaging of serotonin 1A receptor binding in depression. Biol. Psychiatry 46, 1375–1387.

European Monitoring Centre for Drugs and Drug Addiction, 2019. European Drug Report 2019: Trends and Developments.

European Monitoring Centre for Drugs and Drug Addiction, 2020. Statistical Bulletin. European Monitoring Centre for Drugs and Drug Addiction, Lisbon.

Fergusson, D.M., Horwood, L.J., Swain-Campbell, N., 2002. Cannabis use and psychosocial adjustment in adolescence and young adulthood. Addiction 97, 1123–1135.

George, T., Vaccarino, F., 2015. Substance abuse in Canada: The Effects of Cannabis Use during Adolescence.

Grant, B., 1995. Comorbidity between DSM-IV drug use disorders and major depression. J. Subst. Abuse 7, 481–497.

Hall, W., Degenhardt, L., 2007. Prevalence and correlates of cannabis use in developed and developing countries. Curr. Opin. Psychiatry 20, 393–397.

Hartman, et al., 2015. Cannabis effects on driving lateral control with and without alcohol. Drug Alcohol. Depend. 154, 25–37.

Hartman, R.L., Huestis, M.A., 2013. Cannabis effects on driving skills. Clin. Chem. 59, 478–492.

Hasin, D.S., et al., 2016. Prevalence and correlates of DSM-5 cannabis use disorder, 2012-2013: findings from the national epidemiologic survey on alcohol and related condtions-III. Am. J. Psychiatry 173, 588–599.

Hasin, D.S., et al., 2013. DSM-5 criteria for substance use disorders: recommendations and rationale. Am. J. Psychiatry 170, 834–851, 2013*Am J Psychiatry,* Volume 170, p. 834–851.

Hawley, P., Gobbo, M., Afghari, N., 2020. The impact of legalization of access to recreational Cannabis on Canadian medical users with Cancer. BMC Health Serv. Res. 20 (977).

Hayatbakhsh, M.R., et al., 2007. Cannabis an anxiety and depression in young adults: a large prospective study. J. Am. Acad. Child Adolesc. Psychiatry 46, 408–417.

Health Canada, 2019. *Canadian Tobacco, Alcohol and Drugs (CTADS) Survey: 2017 detailed tables.*[Online] Available at: Health Canada. Canadian Tobacco, Alcohol and Drugs (CTADS) Survey: 2017 detailed tables. Available at: https://www.canada.ca/en/health-canada/services/canadian-tobacco-alcohol-drugs-survey/2017-summary/2017-detailed-tables.html#t16. [Accessed 10 July 2020].

Higgins, J.P.T., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analysis. Br. Med. J. 327 (7414), 557–560.

Hill, M.N., Sun, J.C., Tse, M.T., Gorzalka, B.B., 2006. Altered responsiveness of serotonin receptor subtypes following long-term cannabinoid treatment. Int. J. Neuropsychopharmacol. 9, 277–286.

Horsfall, J., Cleary, M., Hunt, G., Walter, G., 2009. Psychosocial treatments for people with co-occurring severe mental illnesses and substance use disorders(dual diagnosis): a review of empirical evidence. Harv. Rev. Psychiatry 17, 24–34.

Hoy, D., et al., 2012. Assessing the risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J. Clin. Epidemiol. 65, 934–939.

Kandel, D.B., Huang, F.Y., Davies, M., 2001. Comorbidity between patterns of substance use dependence and psychiatric syndromes. Drug Alcohol Depend. 64, 233–241.

Kessler, R., 2004. The epidemiology of dual diagnosis. Biol. Psychiatry 56, 730–737.

Khan, S.S., et al., 2013. Gender differences in cannabis use disorders: results from the National Epidemiologic Survey of alcohol and related conditions. Drug Alcohol Depend 130, 101–108.

Khantzian, E.J., 1985. The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. Am. J. Psychiatry 142, 1259–1264.

Lev-Ran, S., et al., 2012. Gender differences in health related quality of life among cannabis users: results from the National Epidemiologic Survey on alcohol and related conditions. Drug Alcohol Depend. 123, 190–200.

Lev-Ran, S., et al., 2014. The association between cannbis use and depression: a systematic review and meta-anlysis of longitudinal studies. Psych. Med. 44, 797–810.

Leweke, F.M., Koethe, D., 2008. Cannabis and psychiatric disorders: it is not only addiction. Addict. Biol. 13 (2), 264–275, 2008 Jun*Addict Biol.,* 13(2), pp. 264-75.

Liberati, A., et al., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann. Intern. Med. 151, W65–W94.

Lin, T., Chapman, S., Hartsig, S., Smith, S., 2015. Potential Health Effects of Legalizing Medical Marijuana in Kansas Kansas Health Impact Assessment Project. Kansas Health Institute, Kansas [Online] Available at. http://www.khi.org/assets/uploads/news/13904/marijuanahia_web.pdf [Accessed 19 November 2020].

Lopez-Quintero, C., et al., 2011. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Drug Alcohol Depend 115, 120–130.

Lynskey, M., et al., 2004. Major depressive disorder, suicidal ideation and suicide attempts in twins discordant for cannabis dependence and early-onset cannbis use. Arch. Gen. Psychiatry 61, 1026–1032.

Lynskey, M., Hall, W., 2000. 20. Lynskey M, Hall W: The effects of adolescent cannabis use on educational attainment: a review. Addiction 2000 95, 1621–1630. *Addiction,* Volume 95, p. 1621–1630.

Marmorstein, N., Iacono, W., 2011. Explaining associations between cannabis use disorders in adolescence and later major depression: a test of the psychosocial failure model. Addict. Behav. 36, 773–776.

Meier, M.H., et al., 2012. Persistent cannabis users show neuropsychological decline from childhood to midlife. In: Proceedings of the National Academy of Sciences of the United States of America (PNAS), 109, pp. E2657–E2664.

Merikangas, K.R., et al., 1998. Comorbidity of substance use disoders with mood and anxiety disorders: results of the International Consortium in Psychiatric Epidemiology. Addict. Behav. 23, 893–907.

Mills, K.L., et al., 2012. Guidelines on the management of co-occurring mental health conditions in alcohol and other drug treatment settings: how useful are they? Ment. Health Subst. Use (5), 160–172.

Moher, D., et al., 2009. Preferred reporting items for sytematic reviews and meta-analyses: PRISMA statement. Open Med. (3), e123–e130.

Murray, R.M., Morrison, P.D., Henquet, C., Di Forti, M., 2007. Cannabis, the mind and society: the harsh realities. Nat. Rev. Neurosci. 8 (11), 885–895.

Offord, D.R., et al., 1996. One year prevalence of psychiatric disorder in Ontarians 15 to 64 years of age. Can. J. Psychiatry 41, 559–563.

Patton, G., et al., 2002. Cannabis use and mental health in young people: cohort study. Br. Med. J. 325, 1195–1198.

Pearson, C., Janz, T. & Ali, J., 2013. Health at a Glance. Mental and substance use disorders in Canada.[Online] Available at: http://www.statcan.gc.ca/pub/82-624-x/2013001/article/11855-eng.pdf [Accessed 04 August 2015].

Regier, D.A., et al., 1990. Comorbidity of mental disorders with alcohol and other drug abuse. JAMA 264, 2511–2518.

Renard, J., Krebs, M.-O., Jay, T.M., Le Pen, G., 2013. Long-term cognitive impairments induced by chronic cannabinoid exposure during adolescence in rats: a strain comparison. Psychopharmacol. (Berl.) 225, 781–790.

Rounsaville, B.J., Dolinsky, Z.S., Babor, T.F., Meyer, R.E., 1987. Psychopathology as a predictor of treatment outcome in alcoholics. Arch. Gen. Psychiatry 44, 505–513.

Salomonsen-Sautel, S., et al., 2014. Trends in fatal motor vehicle crashes before and after marijuana commercialization in Colorado. Drug Alcohol Depend. 140, 137–144.

Sargeant, J.K., Bruce, M.L., Florio, L.P., Weismann, M.M., 1990. Factors associated with 1-year outcome major depression in the community. Arch. Gen. Psychiatry 47, 519–526.

Schauer, G.L., et al., 2016. Toking, vaping, and eating for health and fun: Marijuana use patterns in adults, US 2014. Am. J. Prev. Med. 50 (1), 1–8.

Senn, S.J., 2009. Overstating the evidence – double counting in meta-analysis and related problems. BMC Med. Res. Method. 9 (10).

Silins, E., et al., 2014. Young adult sequelae of adolescent cannabis use: an integrative analysis. Lancet Psychiatry 1 (4), 286–293.

Solowij, N., Pesa, N., 2010. Cognitive abnormalities and cannabis use. Braz. J. Psychiatry 32 (1), S31–S40. Suppl.

Statistics Canada, 2019. *National Cannabis Survey, first quarter 2019.*[Online] Available at: https://www150.statcan.gc.ca/n1/en/daily-quotidien/190502/dq190502a-eng.pdf?st=o9km0p_c [Accessed 17 November 2020].

Stinson, F.S., Ruan, W.J., Pickering, R., Grant, B.F., 2006. Cannabis use disorders in the USA: prevalence, correlates and comorbidity. Psychol. Med. 36, 1447–1460.

Teesson, M., et al., 2012. Prevalence, correlates and comorbidity of DSM-IV cannabis use and cannabis use disorders in Australia. Austr. & N.-Z. J. Psychiatry 46 (12), 1182–1192.

Thomas, G., Kloner, R.A., Rezkalla, S., 2014. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. Am. J. Cardiol. 113 (1), P187–P190.

Tiet, Q.Q., Mausbach, B., 2007. Treatments for patients with dual diagnosis: a review. Alcohol Clin. Exp. Res. 31, 513–536.

Tsou, K., Mackie, K., Sanudo-Pena, M.C., Walker, J.M., 1999. Cannabinoid CB1 receptors are localized primarily on cholecystokinin-containing GABAergic interneurons in the rat hippocampal formation. Neuroscience 93, 969–975.

United Nations Office on Drugs and Crime (UNODC), 2018. *World Drug Report,*Vienna: United Nations Publications.

United Nations Office on Drugs and Crime, 2016. World Drug Report 2016.

van Laar, M., van Dorsselaer, S., Monshouwer, K., de Graaf, R., 2007. Does cannabis use predict the first incidence of mood and anxiety disorders in the adult population. Addiction 102, 1251–1260.

Volkow, N.D., Baler, R.D., Compton, W.M., Weiss, S.R., 2014. Adverse health effects of marijuana use. N. Engl. J. Med. 370 (23), 2219–2227.

Wells, G. A. et al., 2012. *Wells G, Shea B, O'Connell D, Petersen J, The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses.*[Online] Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 4 May 2018].

Whiting, P., et al., 2015. Cannabinoids for medical use: a systematic review and meta-analysis. J. Am. Med. Assoc. 313 (24), 2456–2473.

Wilson, N., Cadet, J.L., 2009. Comorbid mood, psychosis, and marijuana abuse disorders: A theoretical review. J. Addict. Dis. 28, 309–319.

Wittchen, H.U., et al., 1992. Lifetime and six-month prevalence of mental disorders in the Munich follow-up study. Eur. Arch. Psychiatry Clin. Neurosci. 241, 247–258.

Wu, L., Kouzis, A.C., Leaf, P.J., 1999. Influence of comorbid alcohol and psychiatric disorders on utilization of mental health services in the National Comorbidity Survey. Am. J. Psychiatry 156, 1230–1236.