

Exploring the association between cannabis use and depression

Louisa Degenhardt¹, Wayne Hall² & Michael Lynskey³

National Drug and Alcohol Research Centre, University of New South Wales, Sydney, Australia¹, Office of Public Policy and Ethics, Institute for Molecular Bioscience, University of Queensland, St Lucia, QLD, Australia² and Missouri Alcoholism Research Center, Department of Psychiatry, Washington University School of Medicine, St Louis, MO, USA³

Correspondence to:

Louisa Degenhardt
National Drug and Alcohol Research Centre
University of New South Wales
Sydney, NSW 2052
Australia
Tel: +61 29385 0230
Fax: +61 29385 0222,
E-mail: l.Degenhardt@unsw.edu.au

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ABSTRACT

Aim To examine the evidence on the association between cannabis and depression and evaluate competing explanations of the association.

Methods A search of Medline, Psychinfo and EMBASE databases was conducted. All references in which the terms 'cannabis', 'marijuana' or 'cannabinoid', and in which the words 'depression/depressive disorder/depressed', 'mood', 'mood disorder' or 'dysthymia' were collected. Only research studies were reviewed. Case reports are not discussed.

Results There was a modest association between heavy or problematic cannabis use and depression in cohort studies and well-designed cross-sectional studies in the general population. Little evidence was found for an association between depression and infrequent cannabis use. A number of studies found a modest association between early-onset, regular cannabis use and later depression, which persisted after controlling for potential confounding variables. There was little evidence of an increased risk of later cannabis use among people with depression and hence little support for the self-medication hypothesis. There have been a limited number of studies that have controlled for potential confounding variables in the association between heavy cannabis use and depression. These have found that the risk is much reduced by statistical control but a modest relationship remains.

Conclusions Heavy cannabis use and depression are associated and evidence from longitudinal studies suggests that heavy cannabis use may increase depressive symptoms among some users. It is still too early, however, to rule out the hypothesis that the association is due to common social, family and contextual factors that increase risks of both heavy cannabis use and depression. Longitudinal studies and studies of twins discordant for heavy cannabis use and depression are needed to rule out common causes. If the relationship is causal, then on current patterns of cannabis use in the most developed societies cannabis use makes, at most, a modest contribution to the population prevalence of depression.

KEYWORDS Cannabis, depression, marijuana, mood disorders.

INTRODUCTION

The association between cannabis and depression has received much less attention than potential links between cannabis use and psychosis. One reason may be that

depressed cannabis users are much less likely to come to the attention of treatment services than are those who are psychotic. Secondly, cannabis use is an illegal activity and depressed people may not disclose their use voluntarily. Thirdly, there has recently been disagreement as to

whether cannabis dependence (or even problematic cannabis use) existed, little treatment has been available, and the little that has existed may not have detected an association because they have not inquired about symptoms of depression.

In recent years concerns have been raised by rising rates of cannabis use [1–4] and depression [5,6] among young people in many countries. These have been paralleled by an increasing concern about suicide among young adults [7,8], for which problematic drug use and depression are both risk factors [9,10]. Some authors have suggested that cannabis use may be a contributory cause of depression and suicidal behaviours [3,11], an hypothesis which has some suggestive research support. A case-control study in New Zealand found higher rates of cannabis abuse/dependence among those who made serious suicide attempts [16%] than among controls [2%] [9].

WHY EXPECT AN ASSOCIATION BETWEEN CANNABIS USE AND DEPRESSION?

Before considering whether an association between cannabis use and depression exists, we will consider briefly some possible reasons *why* this might be the case. These range from biomedical to the social.

The first is a possible neurobiological link between cannabinoid effects and symptoms of depression. The cannabinoid system, upon which one of the primary psychoactive ingredients of cannabis (delta-9-tetrahydrocannabinol: Δ^9 -THC) acts, appears to be related to the regulation of emotional experience (and therefore of depression). Recent research on mice genetically modified to lack cannabinoid receptors (CB1 receptors), however, has suggested that action at cannabinoid receptors is linked to a *reduction* in depressive behaviours, which implies that that cannabinoids may have an antidepressant action [12].

The second possibility is that an association is in some way socially or demographically mediated. There could be common social or demographic factors that increase the likelihood of both cannabis use and depression. Alternatively, cannabis use (or depression) could cause life events, circumstances or environments that make the other more likely to occur. All these possibilities will be considered later in this paper.

The aims of this paper are to evaluate the existing research evidence on relationships between cannabis use and depression to address the following questions:

- 1 Is there evidence of the association between cannabis use and depression?
- 2 If there is, what are the potential explanations for the association?

3 What evidence is needed to test these different explanations?

4 What are the public health implications of the evidence to date?

In order to examine this issue, a literature search of the Medline, EMBASE and PsychInfo databases was conducted. All references in which the terms 'cannabis', 'marijuana' or 'cannabinoid', and in which the words 'depression/depressive disorder/depressed', 'mood', 'mood disorder' or 'dysthymia' were included, were collected and reviewed. Only research studies were reviewed. Case reports are not discussed in this paper.

ISSUES FACING THE CURRENT REVIEW

Some significant issues faced the review of research on this issue. Different papers use very different measures of mood and cannabis use, as outlined below. Nevertheless, an attempt was made to include all research that addressed the issue, given the scarcity of research on the issue that used (for example) definitions of depression and problematic cannabis use as defined by the American Psychiatric Association's classification system for mental disorders, the *Diagnostic and Statistical Manual* (DSM) [e.g. [13–15].

Furthermore, while it may be expected that those with cannabis dependence would have higher levels of cannabis use, those studies which used measures of the frequency of cannabis use were also judged to be of use in the review, given that if there was a relationship between depression and cannabis use, it was likely to be dose-related. These features of the literature precluded a formal meta-analysis of the relationships between cannabis use and depression.

Measurement of cannabis use

There are the following limitations with the measurement of cannabis use in the research. First, some epidemiological studies have grouped cannabis with other drugs [16,17], so it is not clear what specific contribution cannabis use made. Secondly, some studies grouped cannabis abuse and dependence into 'use disorders' [17], although other epidemiological studies have examined relationships between major depression and cannabis abuse and dependence separately [13,18]. Thirdly, some studies have examined only cannabis *use* without distinguishing between increasing levels of involvement [19–24]. It is important to assess separately the relationships between cannabis use, abuse, dependence and depression.

It is especially important to consider the *level* of cannabis use. It has been most typical to examine patterns of comorbidity between the problematic or regular use of drugs, and other mental health problems, most probably

because (a) it is at higher levels of use that we might expect to see associations with other problems and (b) the clinical concept of comorbidity presupposes the co-occurrence of two *disorders*. It is a reasonable hypothesis that: (a) low-level cannabis use is *not* associated with a *significant* increase in the risk of depression and (b) it is only when people are using cannabis heavily (perhaps weekly or more often) that the risk of depression is increased. The extent to which these hypotheses are borne out is considered below.

Measurement of depression

One issue that has complicated our review of the evidence has been the variety of different ways in which depression has been assessed. Some studies have assessed major depression as defined by DSM while others have used measures of 'depressive symptoms' [25–27], continuous measures of depression [20,28] and cut-off scores on continuous depression scales [29]. It is likely that some of the discrepant findings in the literature reflect these differences in measurement.

EVIDENCE OF COMORBIDITY BETWEEN CANNABIS USE AND DEPRESSION

Comorbidity has been defined by Feinstein as 'any distinct clinical entity that has coexisted or that may occur during the clinical course of a patient who has the index disease under study' [30, pp. 456–7]. Within psychiatry, comorbidity is used commonly to refer to the overlap of two or more psychiatric disorders [31]. However, as shall become apparent below, much of the research on associations between cannabis use and depression have studied only relatively infrequent, low-level cannabis use.

Clinical samples

There is a small literature on cannabis use in clinical populations. In one study of depressed out-patients, a history of substance use disorders was associated with a greater number of depressive episodes [32], but there was no significant difference in age of onset of depression or in severity of depression at assessment [32]. Studies of people with bipolar disorder [33–38] have reported rates of cannabis abuse between 3% [38] and 19% [35]. Among a sample of heroin-dependent people in methadone treatment, daily cannabis users reported the highest rates of depression (compared to occasional and non-users of cannabis) [39,40].

Community samples

Findings from convenience samples in the community have provided conflicting evidence on the association

between cannabis use and depression. One study of a sample of people from a primary care population found that among females only, life-time use of cannabis doubled the risk of depression more than fivefold [41]. One study of a sample of 88 high school seniors found that among cannabis users, greater suicidal ideation existed compared to non-users [42].

In contrast, a study of a volunteer sample of university students aged 19–21 years found no differences between light and heavy users in the number of depressive symptoms they reported [43]. Similarly, a study of high school students found that neither depression nor suicidal ideation were associated with the use of cannabis, tobacco or alcohol [44]. One study used a sample of cannabis users attending college, with two groups: 45 'heavy users' (used cannabis daily for at least 2 years) and 44 'occasional users' (users who had never used cannabis more than 10 times per month) [45]. There were no significant differences between the groups in rates of any psychiatric diagnoses.

A study of male army draftees using cannabis but no other illicit drugs found a relationship between increasing involvement with cannabis use (use, abuse and dependence) and increasing depression scores [28]. However, the study did not compare these patterns to the rates of disorder among draftees who did not use cannabis or to draftees who used cannabis and other illicit drugs, who would presumably form a large proportion of cannabis users [46]. In contrast, there was no association between the frequency of cannabis use and depression among a population sample of young adult males [47].

A study of young adults (aged 20 years) grouped participants according to cannabis use (abstainers, experimenters and 'heavy' users) found that cannabis users had higher levels of depression [20]. However, these groups differed in more ways than their frequency of cannabis use. Heavy users were defined as those who had used cannabis at least 40 times and at least one other illicit drug, experimenters had used cannabis less than 10 times and had not used more than one other illicit drug; abstainers had not used cannabis or any other illicit other drugs.

For several reasons it is difficult to generalize the findings of these studies to the general population. First, some of the samples were extremely small [45]. Secondly, it is unclear how representative the samples were of the populations from which they came. Thirdly, many of the groups sampled were specific populations, such as college students [45], young adult males [47], army draftees [28] or commune members [21]. Fourthly, some studies compared participants who differed in drug use patterns other than cannabis use [19,20], while other studies did not compare cannabis users with non-users [21,28,45] or with those who used other drug types [28].

Representative samples of the general population

Clinical samples are ill-suited to examining the question of whether there is comorbidity between cannabis use and depressive disorders because it is not possible in such samples to distinguish between 'artefactual' and 'true' comorbidity [48]. In order to minimize the effects of sampling and selection biases it is best to study the patterns of association between cannabis use and depression in representative samples of the general population [48–50]. A number of large-scale surveys have examined associations between substance use disorders (including cannabis) and other mental disorders in the United States and other developed countries.

Until recently it was not clear what the relationship was between cannabis use and depression in the two US surveys which shaped much of later psychiatric epidemiological research: the Epidemiologic Catchment Area study (ECA) and the National Comorbidity Survey (NCS). Both reported on associations between 'drug use disorders' (which included cannabis and other substance use disorders) and depression. The ECA found that people who met life-time criteria for DSM-III drug use disorders had rates of life-time DSM-III mood disorders that were between 3.5 and 10.7 times higher than those who did not meet criteria for drug use disorders [17]. The nationally representative NCS found that among those people meeting criteria for life-time DSM-III-R drug abuse and dependence 28% and 39%, respectively, met criteria for a DSM-III-R mood disorder [16].

Recently, Chen and colleagues analysed the NCS data with a specific focus on cannabis use and major depressive episodes [51]. They found that a greater number of occasions of cannabis use were associated with a higher risk of having experienced a major depressive episode; and that life-time DSM-III-R cannabis dependence was associated with a 3.4 times increased risk of major depression: 9.5% of those who had experienced a major depressive episode met criteria for cannabis dependence, compared to 4% of those who had never experienced such an episode [51].

In another major US epidemiological survey of mental health, Grant and colleagues found that people meeting criteria for DSM-IV cannabis abuse or dependence within the past year had 6.4 times the odds of meeting criteria for DSM-IV major depression than those without cannabis abuse/dependence (29% and 14%, compared to 3% overall) [18].

Degenhardt and colleagues examined the relationship between different levels of cannabis use (no use, use, abuse or dependence) and depression in the Australian National Survey of Mental Health and Well-being. They found that those who were more heavily involved with cannabis use were more likely to meet criteria for DSM-IV

mood disorders [13]. Cannabis users were between two and three times more likely to meet criteria for a mood disorder than non-users and the prevalence of such disorders increased from 6% among non-users to 14% among those who met criteria for cannabis dependence.

The findings in adult samples have been mirrored by those in representative samples of adolescents and young adults. Research on drug use and mental disorders in a representative sample of Australians aged 13–17 years found that those who had ever used cannabis were three times more likely than those who had never used cannabis to meet criteria for depression [52].

Fergusson and colleagues examined the association between cannabis use and major depression using data from a birth cohort of 1265 children born in mid-1977 in Christchurch, New Zealand ([15], Ferguson, Horwood & Swain-Campbell 2002). They found that adolescents who had used cannabis 10 or more times by the age of 15–16 years were more likely to also meet criteria for a mood disorder at that age: 11% of those who had never used cannabis met such criteria, compared to 18% of those who had used cannabis one to nine times, and 36% of those who had used it more than 10 or more times [15]. At age 20–21 years, 30% of those who were using cannabis at least weekly met criteria for depression, compared to 15% of those who did not use cannabis at that age (Fergusson *et al.*, unpublished manuscript).

Similarly, the Zurich cohort study of young people (assembled when they were 20 years of age) found that by age 30 years, those who met criteria for depression over the period of the study were 2.3 times more likely to report weekly cannabis use during this time [53].

A study by Patton and colleagues using a representative cohort of young adults (aged 20–21 years) in Victoria found that 68% of females who reported daily cannabis use in the past year were depressed—an odds ratio of 8.6 compared to non-users [29]. No other level of cannabis use was associated with an increased risk of depression and among males there was no association between cannabis use in the past year and depression [29].

In one cohort of American adolescents, those who had experimented with cannabis reported better social adjustment than those who had never used cannabis and those who were heavy cannabis users [19]. This U-shaped curve needs to be considered within its social context: Because this cohort had very high rates of cannabis use, the authors suggested that never having tried cannabis was an indicator of poor social adjustment, anxiety and emotional constriction, as was heavy cannabis use, while experimentation was an indicator of being socially well adjusted [19].

Two other US longitudinal studies have reported conflicting results. Brook and colleagues [54] found no relationship between the involvement with cannabis use and

DSM-III-R depressive disorders over 10 years of follow-up. A study of students aged 12–14 years found that those reporting life-time cannabis use had higher depression scores, and 42% met criteria for DSM-IV major depression at some point in their lives [55].

Summary

There is increasing evidence that regular cannabis use and depression occur together more often than we might expect by chance. While not all studies have found a significant association, the weight of evidence indicates that there is an increased chance of depression among people who report heavy or problematic cannabis use.

WHAT EXPLAINS THE ASSOCIATION BETWEEN CANNABIS USE AND DEPRESSION?

There are a number of ways in which cannabis use and depression might be associated [48,56–58]: (1) cannabis use may be a contributory cause of depression (e.g. cannabis use precipitates depression); (2) depression may be a contributory cause of cannabis use (e.g. if depressed people use cannabis to improve their mood) and (3) there is no direct relationship between the two, with the observed association explained by shared risk factors that increase the risk of both disorders.

Cannabis use causes depression

Popular concerns about the effects of cannabis use on depression often assume implicitly that large doses of the active ingredient of cannabis, Δ^9 -THC, affect serotonin and other neurotransmitters in a way that produces depressive symptoms. There is as yet no animal model to support this hypothesis, but it cannot be excluded.

This is not the only potential mechanism for a causal link between cannabis use and depression. Heavy cannabis use could precipitate depression indirectly by impairing psychological adjustment. That is, it may set in train a cascade of life events, such as early school-leaving and reduced earning capacity, that predispose to depression.

Evidence in support of either hypothesis would include evidence from controlled studies: (a) that cannabis or Δ^9 -THC worsened or did not improve mood; (b) that people who used cannabis in adolescence were more likely to develop depression during a early adulthood; (c) that people who were depressed at baseline are no more likely to become cannabis users during a follow-up period; and (d) that associations between cannabis use and depression were not explained by potentially confounding variables.

Depression causes cannabis use

Perhaps the most popular hypothesis to explain the association between depression and cannabis use is the self-medication hypothesis: that people who are depressed use cannabis to relieve their symptoms of depression [59]. Research on self-reported reasons for substance use provides some support for this idea, e.g. [60], but it can be argued that alleviating dysphoria is simply one among many factors—such as poor social skills, poor social functioning and peer group influences—that increase the likelihood of both substance use and mental disorders [61].

The self-medication hypothesis would be supported by evidence from controlled studies that: (a) cannabis or Δ^9 -THC improves mood; (b) people who are depressed at baseline are more likely to begin, continue or increase their cannabis use during follow-up; (c) people who were cannabis users at baseline are no more likely to become depressed during a follow-up period; and (d) the associations observed in (b) were not explained by confounding variables.

Common factors increase the risk of both depression and cannabis use

The association between cannabis use and depression may arise because the same factors that predispose people to use cannabis also increase their risks of becoming depressed [48,56,59]. These common factors might include biological, personality, social and environmental factors, or some combination of these factors.

This is a plausible hypothesis because there is a wealth of evidence that there are shared risk factors for both mental and substance use disorders. For example, social disadvantage is more common among people who are problematic substance users [61] and who meet criteria for depressive disorders [62–64]. There are also higher rates of separation and divorce, and lower rates of marriage and de facto relationships among people with mental and substance use disorders [62–65]. Other factors that have been associated with both cannabis use disorders and depression include parental psychiatric illness and family dysfunction [66–69].

If common risk factors explain wholly the association between cannabis use and depression then they would no longer be associated when these risk factors were taken into account (e.g. by statistical methods of control). This hypothesis would be supported by controlled studies showing that: (a) the administration of cannabis or Δ^9 -THC did not affect mood; (b) there was no temporal relationship between cannabis use and depressed mood (i.e. that studies did not find that cannabis use predicted depression at a later point in time, and vice versa); and (c) the association between cannabis use and depression did

not persist after statistical control for 'confounding' or 'common' risk factors.

A REVIEW OF RELEVANT EVIDENCE

Studies of the effects of cannabis use upon mood

Recreational cannabis users often report that using cannabis increases well-being, euphoria and contentment [70] but controlled laboratory studies have not shown consistently that regular cannabis use affects mood for better or worse. One study found that cannabis had no effect upon mood in experienced cannabis users, while significantly worsening mood in inexperienced users [71]. Several controlled studies of people with depression have found that Δ^9 -THC significantly increases dysphoria [72,73], while another found that Δ^9 -THC did not improve depressed mood in a small sample of severely depressed in-patients [74].

In a meta-analytical review of the effectiveness of cannabinoids to control chemotherapy-induced nausea and vomiting, Tramer and colleagues found that in the 10 trials that reported rates of this side effect, cancer patients given cannabinoids drugs were eight times more likely to report dysphoria or depression than those given a placebo—overall rates of 13% versus 0.3% [75]. While this is the strongest evidence of an acute adverse effect of cannabinoids upon mood, two issues remain. First, given the population—seriously ill people undergoing intensive treatment for their illness—the generalizability of this result to the general population is questionable; and secondly, an acute effect, while consistent with a causal role of cannabis upon mood, does not necessarily imply a similarly adverse longer-term effect.

Cross-sectional surveys of the general population

In cross-sectional surveys multivariate statistical analysis may be used to examine whether common factors explain the association between cannabis use and depression. In the Australian National Survey of Mental Health and Well-Being (NSMHWB), for example, the relationship observed between cannabis use and depression among adults did not remain significant in multiple regression analyses that adjusted for potential confounders [13]. Specifically, the relationship disappeared after controlling for alcohol, tobacco and other drug use and for neuroticism. This finding suggested that the association arose because cannabis users were more likely to: meet criteria for an alcohol use disorder; to smoke tobacco regularly; to use other drugs; and to have higher neuroticism scores.

In the Australian child and adolescent survey, the increased risks of depression among life-time cannabis users remained significant after statistical adjustment for

confounders but the risk was reduced to two and the lower limit of the 95% confidence interval was close to 1 [52]. Among those who had used cannabis 10 or more times in the past month this association was stronger, with a threefold increase in risk of depression [76].

A weak association observed between early initiation of cannabis use and depression among a sample of adult males was not significant after controlling for educational attainment, marital status, alcohol and tobacco use [47]. Similarly, other research has found that after accounting for demographic characteristics and other drug use, associations between cannabis use and depression no longer remain statistically significant [41].

The use of longitudinal research to examine questions about causality

A more informative way to examine relationship between cannabis use and depression is to conduct longitudinal studies [48,77] in which a sample of people is followed-up over time to examine relationships between cannabis use and depression at one point in time and those relationships at a later time. Evidence from such studies is reviewed in two sections: the first examines whether depression at time 1 predicts cannabis use at time 2; and the second examines whether cannabis use at time 1 predicts depression at time 2. In each case, the 'common cause' hypothesis is examined by multivariate statistical adjustment for confounders.

Does cannabis use predict later depression?

The results of these studies have not been wholly consistent, but most have found that early onset of regular cannabis use predicts an increased risk of later depression.

Among the earliest work was one study by Kandel and colleagues (1986) who followed-up a cohort of adolescents in New York State [26]. They found that cannabis use *per se* at age 15–16 years was not associated with depressive symptoms at age 24–25 years, but greater involvement with cannabis was associated with a lower degree of life satisfaction, and a higher chance of consulting a mental health professional or being hospitalized for a psychiatric disorder [78]. A study of a birth cohort from Dunedin, New Zealand found that cannabis use by age 15 years was not associated with an increased risk of a mental disorder (depression, anxiety disorders, substance dependence or antisocial personality disorder) at age 18 years [79].

The most comprehensive examination of the 'common cause' hypothesis has been reported by Fergusson and colleagues using data on an extremely wide range of possible confounding variables collected on a birth cohort studied from birth to young adulthood [80]. In an early

report, the use of cannabis 10 or more times by age 15–16 years was not associated with either major depression or suicide attempts at age 16–18 years, after controlling for the effects of confounding individual, familial, peer and socio-demographic variables [15].

In contrast, Brook and colleagues found that early-onset cannabis use (use in childhood, adolescence or participants' early 20s, measured on a continuum of use) was associated with a slightly increased risk of major depressive disorder by the age of 27 years, in a longitudinal cohort study of American children [81]. After controlling for demographics, family history and child/adolescent depression, Brook and colleagues found that those who had used cannabis in adolescence had an odds of major depressive disorder 1.17 times those who had not (95% CI 1.04, 1.33). When these relationships were examined by interview periods, Brook and colleagues found that use by the earliest assessment point was related to the strongest increase in risk of major depression (OR 1.57; 95% CI 1.10, 2.22). Those who had first used cannabis in early adulthood did not have any increased risk of major depression by the age of 27 years.

Fergusson and colleagues have re-examined more recently the association between cannabis use during adolescence and depression, suicidal ideation and suicide attempts by age 21 years (Fergusson *et al.*, unpublished manuscript). They examined the effects of heavier patterns of cannabis use than in their earlier study (which used the low cut-off of 10 or more uses in a life-time to define heavy use). They found that by age 20–21 years, 30% of those using cannabis weekly or more often met criteria for depression, compared to 15% of those who did not use cannabis at that age.

Fergusson *et al.* carried out fixed effects regressions that adjusted for socio-demographic and individual factors, adverse life events, peer affiliation, school and home leaving age and alcohol dependence. The adjustments reduced the association substantially, but a significant association remained between cannabis use during adolescence and depression, suicidal ideation and suicide attempts in the same year. After adjustment, use of cannabis weekly or more often in a given year was associated with a 1.7 times greater risk of reporting depression in the same year. For suicidal ideation and suicide attempts, there was an interaction between cannabis use and age: the association between weekly cannabis use in a given year and suicidal ideation/attempts in the same year was highest among those aged 14–15 years. This association declined with age so that by the time the cohort was aged 20–21 years there was no significant association with weekly cannabis use.

Recently, similar analyses have been reported from an Australian cohort of adolescents who were followed into young adulthood to examine the link between early-onset

regular cannabis use and early adulthood depression [29]. This study found that among females only, weekly cannabis use in adolescence predicted a twofold increase in rates of depression at 20–21 years; daily use predicted a fourfold increase in risk. These relationships were adjusted for confounding factors including socio-demographic variables, alcohol use, gender and antisocial behaviour.

The only prospective study examining the relationship between cannabis use and depression in adulthood was reported recently by Bovasso. This study used data from a follow-up of the Baltimore site of the ECA in which a subsample of 1920 people from the original 1980 study were re-assessed 14–16 years later [25]. Those who reported cannabis use and at least one symptom of cannabis abuse/dependence at baseline were 4.5 times more likely to report depressive symptoms and 4.6 times more likely to report suicidal ideation in the follow-up period than those who were 'non-abusers'. This relationship remained after adjusting for baseline depressive symptoms and demographic variables [25]. Approximately 4% of those who reported depressive symptoms during the follow-up period met criteria for cannabis abuse at baseline, compared to 1% of those who did not report depressive symptoms.

Does depression predict later cannabis use?

A number of longitudinal studies of representative samples of children and adolescents, including whole birth cohorts, have examined the association between depression at time 1 and later cannabis use. Generally, these studies have failed to find a significant association.

Kandel and colleagues found no significant relationship between depressive mood and cannabis use either at the same time point, or prospectively over 6 months of follow-up in a cohort of adolescents (16–17 years) from New York State [82]. They did find depressed mood was related to the onset of cannabis use among those who had not used it previously [82]. In a later analysis, Kandel and colleagues reported that depression at age 16–17 years was not associated with higher rates of cannabis use at age 24–25 years [27]. Indeed, males with depression at the first measurement were less likely to have used cannabis than those without a history of depression. Later analyses of this cohort revealed that by age 34–35 years, depression at age 15–16 years was not associated with either early-onset or current heavy cannabis use [83].

A study of a cohort of African American students followed from grade 6 to grade 10 found that depression in 6th grade was not associated with subsequent cannabis use [84]. Similarly, a study of a cohort of Dutch children found that depression did not predict later substance

dependence (including cannabis) [85]. The Dunedin, New Zealand cohort study analysed the relationships between depression at age 15 years and alcohol or cannabis dependence at age 21 years in females in their birth cohort [86]. There was no significant association between the early-onset depression and later cannabis dependence, with or without statistical controlling for covariates.

A longitudinal study of children with prepubertal major depression found that there was no significant association with drug abuse or dependence by the time they were in their mid- to late 20s [87]. The same results were found by Brook and colleagues when they analysed the association between adolescent depression and later cannabis use (ranging from 'light' to 'heavy'), after controlling for age and gender [54]. Most recently, Patton and colleagues analysed the strength of association between depression between ages 14–18, and use of cannabis either weekly or daily at age 20–21 years [29]. There was no significant relationship between adolescent depression and young adult weekly or daily cannabis use after adjusting for sociodemographic variables, alcohol use, gender, adolescent cannabis use and antisocial behaviour. The Bovasso study also found that among those who did not meet criteria for cannabis abuse at baseline, depressive symptoms at baseline did not significantly predict an increased risk of cannabis abuse during follow-up [25].

Summary

Cross-sectional and longitudinal studies have provided mixed evidence on the nature of the association between cannabis use and depression. Cross-sectional studies have suggested that the relationship can be explained by other factors such as the use of other drugs. Longitudinal studies have consistently indicated that the 'self-medication' hypothesis does not fit the pattern of cannabis use over time among cohorts of adolescents and young adults. There is more mixed evidence that heavy cannabis use increases the risk of depression during follow-up, and this relationship is partly but not explained completely by confounding variables.

The Bovasso study [25] allows some estimation of the population attributable risk for this association. Approximately 67% of those with cannabis abuse but no depressive symptoms at baseline developed depression during 14–16 years of follow up, compared to 31% of those without cannabis abuse. It is not clear why Bovasso examined only cannabis abuse, and not dependence. The number of people who met criteria for cannabis abuse at baseline without also reporting depressive symptoms was extremely small (only 15 of 849 who did not report depressive symptoms at baseline).

As a result, 0.6% of the sample developed depressive symptoms in the 14–16 years after using cannabis and possibly as a consequence of their cannabis use. These figures are likely to be overestimates of the effect of problematic cannabis use as they assume a strong causal relationship when a variety of potentially confounding factors were not assessed in the Bovasso study, including non-diagnostic scale measures of depression. Given current rates of cannabis use, assuming that the link is causal, then 1.9% of the depressive symptoms that developed over 15 years could be attributed to cannabis abuse. Thus, in a population in which problematic cannabis use is uncommon (as is still the case in most developed countries) then heavy cannabis use plays a minor role in explaining population rates of depression.

IMPLICATIONS FOR FUTURE RESEARCH

Our review of the literature has identified a number of limitations in the available research on cannabis use and depression. In the following section we outline these limitations, and suggest ways in which future research might overcome them.

Measurement of cannabis and depression

Given the widely varying measurement of both cannabis use and depression, it is possible that differences in findings have resulted from these differences. Future research needs to assess exposure to cannabis more effectively.

Study designs

Convenience samples are not appropriate for examining associations between cannabis use and depression [49]. Well-designed surveys of the general population have indicated that heavy cannabis use and depression occur at a level greater than chance, but these studies are less well-suited to testing causal hypotheses. Two study methods that are more appropriate for this task are longitudinal studies [80] and analyses of data from genetically informative research designs [57,88]. Controlled studies of the effects of cannabis on mood would provide the strongest level of evidence on the role of cannabis in mood states.

Longitudinal studies

Almost every longitudinal study conducted to date has been on adolescents or young adults. From a public health perspective, this group is the one most 'at risk' because it has the highest rates of cannabis use. None the

less, we also need to study relationships between cannabis use and depression among older adults, especially as more of the birth cohorts that initiated use in the 1970s continue to use cannabis into middle age. Such an examination could test whether the association is due to relationships that are independent of age. This may not be the case (Fergusson *et al.*, unpublished manuscript). The one study that was conducted with a sample of adults was limited by the number of participants in some groups (only 15 participants were 'cannabis abusers' without depressive symptoms at baseline), and the lack of precision about events that occurred during the long follow-up period (a 14–16 year interval between baseline and follow-up) [25]. More temporally detailed long-term studies of this relationship are required in adults.

The use of genetically informative designs to examine causality

No longitudinal studies have examined the possibility that common or correlated genetic predispositions to use cannabis or become depressed may explain the comorbidity between depression and cannabis. This hypothesis is supported by mounting evidence for a substantial genetic component in many behaviours and behavioural disorders, including both cannabis dependence and depression [88,89]. Twin studies have reported a moderate to high heritability of both cannabis use/dependence and liability to depression. Specifically, estimates of the heritability of cannabis dependence have ranged from 45% to 62% [90–92] and a recent meta-analysis of twin studies of major depression has suggested that 37% of the liability to major depression is due to heritable factors [93]. A recent study suggests that the association between major depression and cannabis dependence may be explained partially by a high degree of overlap in the genetic factors predisposing to cannabis use and depressive disorders [94].

Given these findings, genetically informative research designs may in future make substantial contributions to understanding the relationship between cannabis use and depression. These research designs include the study of twins, either reared together or apart, adoption studies, studies of the children of twins and other extended family designs. Studies of twins who are discordant for cannabis use or depression would be especially informative. A range of these study designs (recently summarized by Rutter *et al.* [88]) need to be applied to the study of the relationship between cannabis use and depression. The need for more of such research is reinforced by recent findings that much of the association between depression, and both tobacco [95] and alcohol [96] dependence, can be explained by common genetic factors.

CONCLUSIONS

Surveys of representative samples of the general population have established that rates of depression are elevated in those who use cannabis frequently or who are cannabis dependent. The extent of this comorbidity exceeds levels we would expect to see by chance. There does not appear to be an increased risk of depression associated with infrequent cannabis use.

The reasons for this comorbidity are unclear. Research to date does not support the self-medication hypothesis. It is too early to rule out shared risk factors because cross-sectional studies that have controlled for confounding variables have found that the relationship disappears while results from cohort studies have been more mixed.

There is a modest association between early-onset regular or problematic cannabis use and later depression in several well designed longitudinal studies. There are at least two broad classes of explanation: the first of these is the biological hypothesis that cannabis use causes changes in neurotransmitter systems that make depressed mood more likely. There is little research evidence to support this possibility directly. Better evidence supports the alternative form of this causal hypothesis, that the effects of regular or problematic cannabis use are socially mediated. There is increasing evidence that regular and early-onset cannabis use are associated with reduced educational attainment [97], unemployment and crime [15,97], all factors that may increase risks of later mental health problems. However, the evidence on this issue is limited, and future research needs to examine both possibilities.

There is a need for longitudinal and twin studies that assess more effectively the relationship between cannabis use, depression and confounding factors. There is also a need to examine relationships between these variables in adult samples, as associations to date have only been reported for adolescents or young adults.

If we assume that cannabis use and depression are causally related, the proportion of depression that is attributable to cannabis use is modest. On the basis of the current literature, and on current patterns of cannabis use in the general population (in which few people use cannabis heavily), regular cannabis use explains only a small proportion of depression in the population.

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