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Cannabis and Mental Health: Put into Context

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Cannabis and Mental Health: Put into Context

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Executive Summary

Cannabis and mental health problems—particularly psychosis—have gained substantial attention worldwide in the last five years. This prominence is due to recent, good research on the link between cannabis and psychosis. This monograph provides a review of this and previous research.

The term 'psychosis' refers to a set of signs and symptoms that impair someone's ability to remain in touch with reality, often characterised by hallucinations (sensations that have no apparent cause) and delusions (beliefs that are not grounded in reality). It should be noted that discrete psychotic *symptoms* (e.g. a hallucination during fever) can be experienced without necessarily being part of a psychotic *disorder*, and that such symptoms can occur briefly, without ongoing problems. When symptoms of sufficient number and severity occur for a specified time, then a psychotic disorder, such as schizophrenia, may be diagnosed. While psychosis is commonly associated with schizophrenia, it may be present in other mental health disorders.

A number of factors appear to contribute to the development of psychotic disorders. These factors include genetic variations, birth complications, and environmental factors such as place and season of birth. Some drugs, such as alcohol, amphetamines, cocaine and cannabis, appear to increase the risk of psychotic symptoms, or to make existing symptoms of psychosis worse.

There is consistent evidence from cross-sectional research, undertaken on a group of people on one occasion, that cannabis use and schizophrenia occur together more often than would be expected by chance. Additionally, the major cohort studies assessing the relationship between cannabis and schizophrenia over time found a relatively consistent relationship between cannabis and psychotic *symptoms*, but only a minority of the studies reported a significant relationship between cannabis use and the subsequent development of a psychotic *disorder*. The distinction between psychotic symptoms and a diagnosable mental health disorder is important, as psychotic symptoms are reported by many people who would never be diagnosed as psychotic and for whom their impact is minimal.

The use of cannabis in Australia has increased considerably in the past fifty years, yet there is no evidence of a corresponding increase in the incidence of schizophrenia. The contentious question of whether cannabis use can cause serious psychotic disorders that would not otherwise have occurred can only be answered partly. It is quite likely that cannabis use has precipitated some mental health problems. However, the number of cases that would not have otherwise occurred is small.

Having a family history of schizophrenia is associated with the greatest relative risk for subsequent hospitalisation for schizophrenia. In contrast, birth in an urban area appears to account for the greatest number of cases of schizophrenia in the population, but it is unclear what the reasons are for this effect. Heavy cannabis use in adolescence ranks as the third most significant risk factor for schizophrenia in terms of both measures. It is likely that many causal factors interact to produce schizophrenia, and that different factors are involved in different cases.

Two other categories of mental illnesses associated with cannabis use are mood disorders such as depression and bipolar disorder, and anxiety disorders. Mood and anxiety disorders can often co-occur and are much more common than psychotic disorders in the population. Approximately one in four people develop an anxiety disorder, and depression affects up to 25% of women and 12% of men.

Research assessing the link between cannabis and mood and anxiety disorders has received less attention than the research assessing cannabis use and psychotic disorders. There is evidence that early, frequent and continued cannabis use may increase the risk of depression in adulthood. The research on bipolar disorder is sparse, results are mixed, and alternative explanations for the relationship exist. While much research is available on anxiety and cannabis use, the evidence for a causal relationship is also inconclusive.

Other negative effects associated with cannabis use include the deleterious effects associated with smoking, the cost, which is probably elevated due to its illegality, and the substantial risk of cannabis dependence. Cannabis use is associated with an increased probability of other illicit drug use, engaging in criminal activity, poorer educational attainment and employment prospects, and other social outcomes. Finally, there are a number of sensory, cognitive and motivational deficits that have been linked to heavy cannabis use.

Although there is still some uncertainty about the nature of the relationship between cannabis use and mental health disorders, the following conclusions can be drawn:

1. Current evidence indicates that cannabis use can contribute to the onset of schizophrenia and that there may be cases that would not have emerged without such use. The number of such cases is unknown and may be small. The effect of cannabis in this regard is probably additive with other risk factors. Individuals with known or suspected risk factors for schizophrenia should be advised to avoid its use. The conclusion of Hall, Degenhardt and Teesson [1], “a vulnerable minority [of individuals diagnosed with schizophrenia] appear to be at increased risk of experiencing harmful outcomes” (p 441), sums up the situation well.

2. The association between cannabis use and later experience of psychosis (either symptoms or disorders) appears to be stronger with increasing quantity and frequency of use, and early initiation of use. Young people need to be aware of this association.

3. Other adverse outcomes associated with cannabis, such as dependence, financial cost/hardship, poorer educational achievement and employment prospects, are also more likely the younger the person is when they begin to use cannabis.

4. There is some evidence that cannabis use is associated with an increased risk of depression, particularly with long-term, frequent use and early initiation of use. These risks may be greater for females.

5. The use of many psychoactive substances is likely to have adverse effects on those experiencing a mood or anxiety disorder.

6. It is unlikely that eliminating the supply of cannabis, if this could be accomplished, would eradicate the motivation to use it. Most cannabis users report that they would substitute another drug, usually alcohol, in its absence.

1 Introduction

1.1 Cannabis and mental health: The debate

In this document, the term “cannabis” is used to describe any psychoactive product of the plant *Cannabis sativa*. Evidence has shown that those experiencing mental health disorders use cannabis at higher rates than those who are not experiencing mental health disorders, and, conversely, that cannabis users are more likely to experience mental health problems than their non-cannabis-using peers [2]. However, the reason for this association remains unclear; it is unknown whether cannabis causes mental health problems, whether mental health problems make it more likely that someone will use cannabis, or whether there is a third factor that influences both. Determining the nature of the link between the use of a substance and a particular adverse health outcome is an essential step in assessing the social and economic burden of that substance use [3].

Interest in the association between cannabis and mental health has a long history. In the mid-19th century the French psychiatrist Jacques-Joseph Moreau (1845/1973) [4] documented the effects of cannabis intoxication in volunteers and claimed that such intoxication could reproduce nearly any mental disturbance. In India, in 1893 a Commission was created by the British government to investigate potential consequences of cannabis use, including psychosis; cannabis-induced psychosis was seen as a common occurrence in India at the time, although the commission concluded that this effect was greatly exaggerated [5]. In the United States in the 1930s, newspaper stories of cannabis users becoming mad and homicidal appeared (‘reefer madness’), and were taken to Congress by the Federal Bureau of Narcotics [6]. However, by the 1960s, the issue of cannabis and mental health problems was no longer receiving as much attention in the United States and other Western countries as it had previously [7].

More recently, there has been a surge of interest world-wide in the link between cannabis and mental health—particularly psychosis [8][9]. Prior to the late 1980s, it was not possible to establish whether cannabis contributed significantly to mental health problems due to the inadequate methodology of the studies conducted [10]. In 1987, the first large cohort study (i.e. a well defined sample studied over time) assessing the link between cannabis and psychosis was published [11]. The current interest in the link between cannabis and mental health is due in part to the release of similar high quality cohort studies [12][13][14][15], and has focused attention on cannabis here in Australia and overseas. The UK Home Office ordered an investigation into the links between cannabis and mental health in order to determine whether cannabis should be re-categorised into a more serious drug class [9]. The United Nations Office on Drugs and Crime recently paid special attention to cannabis in their 2006 World Drug Report [16].

Australia’s first National Cannabis Strategy was endorsed by all Australian Government and State and Territory Health and Law Enforcement Ministers on 15 May 2006. [17] The following year, the Australian Government established the National Cannabis Prevention and Information Centre (NCPIC). NCPIC is run by a consortium of key organisations, led by the National Drug and Alcohol Research Centre, and is situated at the University of New South Wales. The aim of this centre is to reduce the use of cannabis in Australia by preventing

uptake and providing the community with evidence-based information and interventions. Key strategies include a multimedia (website, pamphlet, bulletin, and other resources) based approach to dissemination of evidence-based information on cannabis; an intersectoral workforce training program; intervention development and evaluation; and the provision of a free national Cannabis Information and Helpline (1800 304050) for cannabis users, their families and the community.

1.2 Cannabis and mental health: Put into context

Despite a number of recent reviews assessing the link between cannabis and mental health [18][19][20], there is still confusion among the general public and policy makers alike. The aim of this monograph is to attempt to provide clear information about cannabis and mental health. It does not simply review research on cannabis and mental health. Although the monograph provides an overview of what the research says about the link, it will place this research in a broader context. Some of the questions this monograph will aim to answer include:

- Does cannabis use lead to mental health problems, and if so, which ones?
- If someone smokes cannabis are they at risk of developing mental health problems that would not otherwise have occurred?
- What is the contribution of cannabis to mental health problems compared to other drugs and alcohol?
- How does cannabis compare to other mental health risk factors?
- What is the population impact of cannabis with respect to mental health?
- What are the policy implications of the relationship between cannabis and mental health?

This monograph was written primarily for use in public policy to provide a clear understanding of what the research says about the link between cannabis and mental health in order to guide policy. The monograph may also be useful for those working in the field of alcohol and other drugs, the media, politicians and interested members of the general community. This monograph focuses on the mental health effects of cannabis use; for a review of other aspects of cannabis use, supply and harms, as well as a discussion of the legislative status of cannabis in Australia, see the recent National Drug Strategy monograph *Cannabis in Australia: Use, supply, harms and responses* [21], or *The health and psychological effects of cannabis use* [22]. Another recent text is *Cannabis use and dependence: Public health and public policy* [2]. Potential harms other than adverse mental health outcomes that are also associated with cannabis use and may be more common include dependence, social and interpersonal problems, educational and vocational failure and cognitive dysfunction. These harms should be recognised as important alongside the mental health harms, in spite of the greater amount of attention focused on the latter [23].

It is essential to state how the literature to be reviewed has been evaluated. Studies in this review were evaluated against the conventional criteria of strong covariance (cannabis use and the disorders occur together), temporal precedence (cannabis use precedes the onset of mental health disorders), absence of alternative causal mechanisms (nothing else causes cannabis use and/or the disorders) and coherence with current knowledge (the way in which cannabis affects mental health disorders is consistent with what we know about both) [24].

Studies are then further assessed for methodological adequacy. In brief, important factors that have been considered include the population from which the samples have been drawn and the sample size, whether alternative causal mechanisms for the mental health disorder were controlled for, the appropriateness of the measurement tools used and the types of outcomes that the study evaluated. Finally, we attempted to estimate the magnitude of the effect of cannabis use on the occurrence of mental health disorders to place it in the context of other public health concerns.

2 Cannabis use: Epidemiology and risk factors

2.1 Cannabis dependence: Definition

Although many people will try cannabis at some point during their lives, most people do not progress to chronic, long term use. Most will experiment sporadically with cannabis during adolescence and early adulthood and cease use once reaching their mid- to late-20s [25]. However, there is a proportion that will use cannabis more often, for a longer period of time, and develop cannabis dependence. It has been estimated that approximately one in ten people who use cannabis once will become dependent [2]. For those that have used several times, the risk of dependence is about one in five, and for daily users the risk is one in two. Those who are dependent on cannabis are at a greater risk of experiencing the harms associated with cannabis use. Dependent cannabis users report cognitive and motivational problems, interpersonal relationship problems, memory deficits, and financial difficulties, all of which they associate with their dependence [26].

In the past, cannabis dependence was considered mild or non-existent. Its slow clearance from the body did not elicit an obvious withdrawal state like heroin or alcohol. The discovery of the brain's cannabinoid system led to research that clearly showed cannabis withdrawal in animals [27]. Surveys of cannabis users [28] and laboratory studies [29] revealed cannabis tolerance (i.e. requiring increasingly greater amounts of a drug to obtain the desired psychoactive effect) as well as withdrawal. The two major diagnostic instruments—the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the International Classification of Diseases (ICD-10) recognise these signs of dependence and specify diagnostic criteria for cannabis use disorders (see Boxes 2.1 & 2.2).

Box 2.1: Diagnostic Criteria for cannabis use disorders

Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision

Cannabis Abuse:

A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by at least one of the following, occurring within a 12-month period:

   (1) Recurrent cannabis use resulting in a failure to fulfil major role obligations at work, school, or home

   (2) Recurrent cannabis use in situations in which it is physically hazardous

   (3) Recurrent cannabis-related legal problems

   (4) Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis

B. The symptoms have never met the criteria for Cannabis Dependence

Cannabis Dependence:

A maladaptive pattern of cannabis use, leading to clinically significant impairment or distress, as manifested by at least three of the following occurring at any time in the same 12-month period:

(1) Tolerance, as defined by either of the following:

   (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect

   (b) markedly diminished effect with continued use of the same amount of the substance

(2) Withdrawal, as manifested by either of the following:

   (a) the characteristic withdrawal syndrome for cannabis

   (b) cannabis, or a cannabis-like substance is taken to relieve or avoid withdrawal symptoms

(3) Cannabis is often taken in larger amounts or over a longer period than was intended

(4) A persistent desire or unsuccessful efforts to cut down or control cannabis use

(5) A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects

(6) Important social, occupational, or recreational activities are given up or reduced because of cannabis use

(7) Cannabis use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cannabis

From the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision [30]

Box 2.2: Diagnostic Criteria for cannabis use disorders

ICD-10 Classification of Mental and Behavioural Disorders

Cannabis Dependence Syndrome

Three or more of the following manifestations should have occurred together for at least one month or, if persisting for periods of less than one month, should have occurred together repeatedly within a 12-month period:

(1) a strong desire or sense of compulsion to take the substance;

(2) impaired capacity to control cannabis-taking behaviour in terms of its onset, termination, or levels of use, as evidenced by: cannabis being often taken in larger amounts or over a longer period than intended; or by a persistent desire or unsuccessful efforts to reduce or control substance use;

(3) a physiological withdrawal state when cannabis use is reduced or ceased, as evidenced by the characteristic cannabis withdrawal syndrome, or by the use of cannabis or similar substances with the intention of relieving or avoiding withdrawal symptoms;

(4) evidence of tolerance to the effects of cannabis, such that there is a need for significantly increased amounts of cannabis to achieve intoxication or the desired effect, or a markedly diminished effect with continued use of the same amount of cannabis;

(5) preoccupation with cannabis use, as manifested by important alternative pleasures or interests being given up or reduced because of cannabis use; or a great deal of time being spent in activities necessary to obtain, take or recover from the effects of cannabis;

(6) persistent substance use despite clear evidence of harmful consequences, as evidenced by continued use when the individual is actually aware, or may be expected to be aware, of the nature and extent of harm.

Harmful Cannabis Use

A. There must be clear evidence that cannabis use was responsible for (or substantially contributed to) physical or psychological harm, including impaired judgement or dysfunctional behaviour, which may lead to disability or have adverse consequences for interpersonal relationships

B. The nature of the harm should be clearly identifiable (and specified)

C. The pattern of use has persisted for at least one month or has occurred repeatedly within a 12-month period

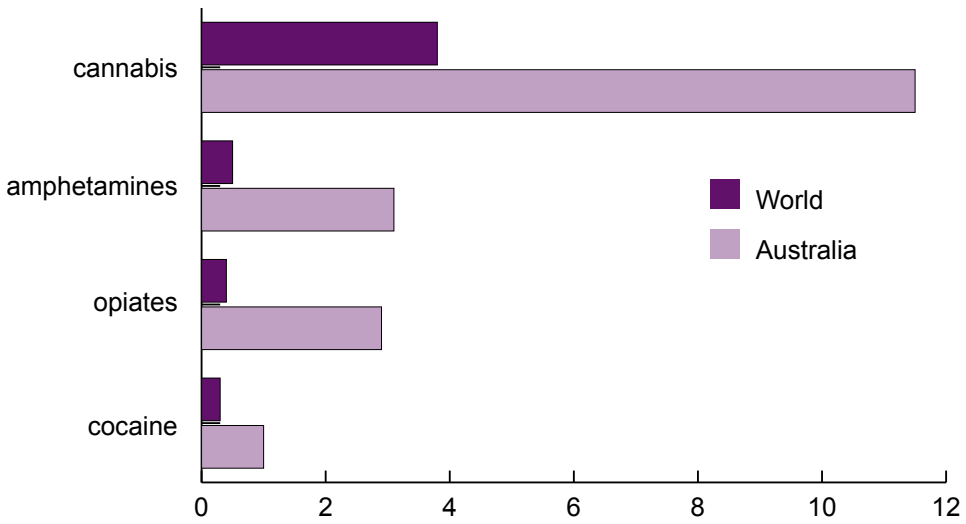
D. The disorder does not meet the criteria for any other mental or behavioural disorder related to the same drug in the same time period (except for acute intoxication).

From the International Classification of Diseases, tenth revision,
Classification of Mental and Behavioural Disorders, World Health Organization, 1993

2.2 Prevalence and patterns of use

Of the illicit substances in Australia, cannabis is the most widely used in the world; the United Nations Office on Drugs and Crime (UNODC) estimated that almost 160 million people worldwide used cannabis in 2005 [16]. This far outweighs the number of users of all other illicit substances put together (Figure 2.1). When comparing the use of cannabis, amphetamines, opiates and cocaine in Australia in 2004 [31] it is apparent that the proportion of Australians who reported using cannabis at least once in 2004 (11.3%) is about three times that of the world proportion in 2005 (3.8%).

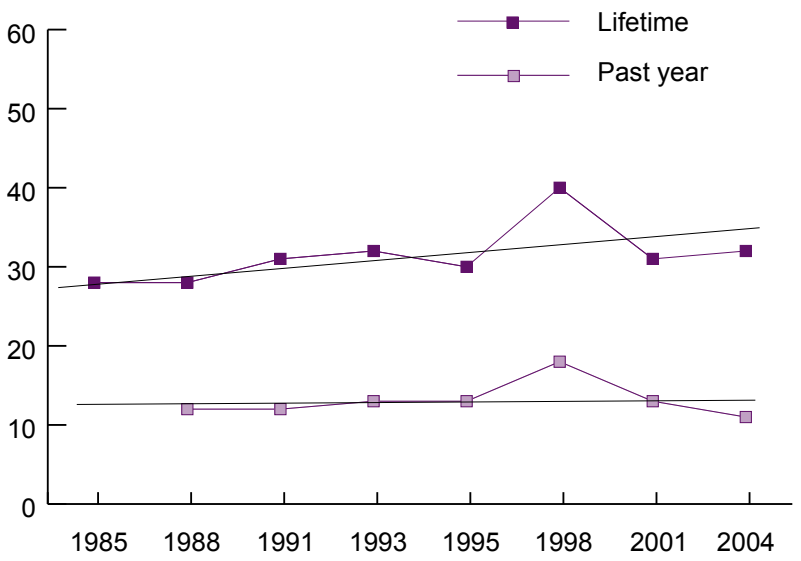
Figure 2.1: Percent of people aged 15–64, who used these illicit drugs at least once in 2005 (United Nations Office on Drugs and Crime, 2007) or aged 14 and over in Australia in 2004 (AIHW, 2005)



In the United States of America (USA), the United Kingdom (UK) and Australia, the past-year prevalence of cannabis use may have declined slightly in recent years, although there are some methodological issues that may have contributed to the apparent decline. For example, in Australia, interviews are now conducted over the telephone, whereas they were previously conducted face-to-face. Both Aquilino [32] and Gfroerer and Hughes [33] found substantially lower rates of illicit drug use in a telephone interview format when compared to a face-to-face format.

From the first surveys in the 1970s, the use of cannabis in Australia increased steadily until at least 1998. Even with the recent decline in use, it remains the most widely used illicit drug in Australia. According to the most recent National Drug Strategy Household Survey, approximately one-third of Australians have tried cannabis, and about one in ten have used it in the past year [31]. Cannabis use is most prevalent among those aged in their 20s, and is more commonly used by males than females.

Figure 2.2: Lifetime and past year prevalence of cannabis use in Australia, 1985–2004. (Source: National Drug Strategy Household Survey)



Use of cannabis has fallen since an apparent peak in 1998 [34]. The rise in lifetime use in Figure 2.2 can be explained by about 1 in 15 cannabis users ceasing use each year.

2.3 Risk factors for cannabis use and dependence

2.3.1 Reasons for cannabis use

The subjective effects of cannabis typically include; an initial non-specific sensory "buzz" or "rush", euphoria and relaxation, labile mood (especially inexplicable mirth), altered sensory perceptions (usually perceived as enhanced), an increased focus on imagination and a reduced focus on the self. Most users find these effects pleasant, while a minority become disturbed, particularly if they interpret the sensory and cognitive alterations as pathologic. The effects are dependent upon both the route of administration and dose. The initial "buzz" seems more common with smoking and is probably due to the faster transfer of cannabinoids to the brain. High doses or lack of experience are usually implicated in producing negative effects, particularly those including disturbing sensory alterations or feelings of depersonalisation. A number of other acute effects such as drowsiness and increased appetite are less likely to be reasons for recreational use.

Gaining an understanding of the reasons why people use cannabis, or their motives for use, may help inform prevention and intervention programs [35]. Research into reasons for cannabis use has typically used two methods: collecting self-generated reasons for use using open-ended questions, or asking about specific reasons for use using the Marijuana Motives Measure (MMM) [36]. The MMM is a measure derived from the 20 item

Alcohol Motives Measure [37] by adding five statements concerning the consciousness enhancing qualities of cannabis to that measure and altering the wording by substituting "use marijuana" for "drink". Items are endorsed by frequency, from "Almost never/never" to "Almost always/always". The MMM groups motives to use cannabis into five categories; enhancement (the positive effects of cannabis—to 'get high'), coping (dealing with negative moods, such as depression and anxiety), social (facilitating socialisation), conformity (group identification/peer pressure) and expansion (cognitive and perceptual enhancement).

A study of American university students found that, of those who had used cannabis during their lifetime, enhancement and social motives were most commonly endorsed; conformity motives were the least common motives reported [36]. Using multiple regression analysis, it was found that enhancement and coping significantly predicted cannabis use in the past six months with coping being a better predictor for females. Social motives predicted cannabis use problems.

A study using a sample of adolescents and young adults found that among males, enhancement motives were associated with higher frequency of cannabis use, and among females, expansion motives were associated with both higher frequency of use and cannabis dependence [38]. Symptoms of anxiety and depression did not significantly predict frequency of cannabis use in this study, but in males borderline personality scores predicted dependence. This suggests that self medication of depression and anxiety is not the main determinant of frequency of cannabis use in adolescents and young adults.

Similarly, in another sample of American college students cannabis use was predicted by enhancement motives [39], replicating the above study [38]. Cannabis-related problems were related to both impulsivity and using cannabis to cope with negative mood.

Another recent study found that all MMM factors except for conformity predicted frequency of cannabis use, with enhancement motives having the strongest relationship, replicating the earlier work [40]. This study also found that cannabis users with higher levels of anxiety sensitivity than their peers were more likely to use cannabis due to the perception that it may reduce, or manage, negative emotional distress. Cannabis users with high levels of anxiety sensitivity are more likely to experience serious symptoms of anxiety, such as panic attacks [41]. If those who are prone to anxiety tend to use cannabis to alleviate unpleasant sensations, their risk of experiencing symptoms of anxiety may be compounded by their cannabis use over the long-term, leading to a cycle of worsening anxiety [40][42]. Buckner et al. [44] found a similar pattern of associations between motives and cannabis use, but noted that problems attributed to cannabis were more closely related to social anxiety and obsessive–compulsive behaviours than anxiety sensitivity. It should be noted that reports of increased anxiety when cannabis users are observed have not been replicated when users self-report and are not directly observed [43].

Comeau and colleagues [45] sampled a younger population than most other researchers, with a mean age of just over fifteen years. As only those who acknowledged use of a substance completed the relevant measures of motivation, it was not possible to test associations between motives and usage. Anxiety sensitivity scores were associated with endorsing conformity motives for cannabis use. As this study used an instrument that did not assess expansion motives, the results should be interpreted with some caution.

One criticism of the MMM is that it has been adapted from a measure of alcohol use motives, and although cannabis-specific motives were added, these may not capture all the motives that are unique to cannabis. Recently, Lee and colleagues [46] examined self-generated reasons for cannabis use in 634 students about to enter college. Nineteen distinct motives for cannabis use were identified: enjoyment; conformity; experimentation; social enhancement; boredom; relaxation; coping; availability; perceived low risk; altered perception; activity enhancement; rebellion; alcohol intoxication; food enhancement; anxiety reduction; image enhancement; celebration; medical use; and habit. The first six of these reasons for cannabis use were the most highly endorsed, in descending order. Using multiple regression, it was found that experimentation was associated with less use and problems, whereas habit was associated with more frequent use and coping was associated with more problems [46].

It is apparent that the motives for using cannabis are numerous and vary widely between users. This should alert us to the complexity of the effects of cannabis. Such an insight may help to understand the sometimes contradictory findings to be reviewed.

Table 2.1: Studies of reasons for substance use

Study	Sample	Cannabis use measure	Motives measure	Most commonly endorsed reasons	Predictors of use			
					Recent cannabis use	Cannabis frequency	Cannabis problems	Cannabis dependence
Simons et al. (1998)	161 American university students	Cannabis use in the past six months	MMM	Enhancement and social	Enhancement and coping (coping stronger for females)		Social and conformity	
Comeau, Stewart & Loba (2001)	508 Canadian secondary students	Ever used	TMMQ	Enhancement and social				
Chabrol et al. (2005)	212 French adolescents and young adults	Cannabis use in the past six months	MMM			Enhancement (males); expansion (females)		Expansion (females)
Simons et al. (2005)	309 American university students	Cannabis use in past 12 months	MMM		Enhancement and coping motives		Coping motives	
Bonn-Miller, Zvolensky & Bernstein, (2007)	141 American young adult females	Current cannabis use	MMM	Enhancement and social		Enhancement, social, coping and expansion		
Buckner et al., (2007)	159 American university students	Ever used cannabis	MMM			Enhancement, expansion, coping, social and conformity	Expansion, enhancement, coping and social	
Lee, Neighbors & Woods, (2007)	634 American students entering college	Ever used cannabis	Open ended	Experiment, enhancement	Habit, enhancement, experiment, expansion, enjoyment and sex		Coping, habit, enjoyment, expansion, enhancement and experiment (–)	

Among the studies using the MMM as an assessment of motives to use cannabis, it is clear that enhancement and expansion motives are related to cannabis use and social and coping motives are related to problems attributed to cannabis. Simons et al. [39] reported that motives increasing the frequency of cannabis use might indirectly lead to cannabis-related problems, since frequency of cannabis use was related to both motives to use cannabis and cannabis use problems. In the same study, cannabis problems were directly predicted by using cannabis to cope with negative mood.

Overall, it appears that cannabis users commonly cite enhancement of their activities and improved social relations as the primary motivations for continued use. Using cannabis to cope with negative mental states seems to be the most common motive associated with problems attributed to cannabis, with social and conformity motivations also contributing.

2.3.2 Reasons for cannabis use among those with existing mental health disorders

Reasons for cannabis use among those with a mental health problem are important in defining the causal relationship between the two, given that those with a mental health disorder are two to three times more likely to have a concurrent substance abuse problem [47]. Cannabis, like many other drugs, can exacerbate existing mental health problems, and it may be that those with a mental health disorder are particularly sensitive to the negative effects of cannabis [48]. While it has often been asserted that psychoactive recreational drugs are taken by those with mental health disorders to diminish the symptoms of the disorder [49] or the side effects of medication, it is disputed whether the anxiolytic or euphoric effects of such drugs are any more potent in those with mental health disorders [48][cf. 50]. However, those with mental health disorders are disproportionately likely to have common risk factors for recreational drug use such as unemployment, boredom, poverty and deviant social networks. Casual cannabis use by those with mental health disorders may be motivated by similar reasons to those reported by the general population.

Both research studies [51][52][53][54][55] and reviews [56][57] of the expressed reasons for cannabis use among those experiencing psychoses indicate that their reasons, while very similar to those of non-psychotic respondents, give more weight to reducing dysphoria, boredom and of course specific psychotic symptoms. Those abusing cannabis, as judged by the criteria of Drake et al. [48] were more likely to cite self-medication as a reason.

2.3.3 Awareness of the risks of cannabis use

The mental health risks of using cannabis are usually acknowledged by those with [52] and without [58] mental health problems, whether they are cannabis users or not. However, the perception of such risks varies greatly from complete ignorance or denial to risk perception far beyond what is warranted by the available evidence. While some individuals may be deterred from using cannabis by increased perception of risk [59], attempting to persuasively inflate such perceptions may have no effect in the population [60]. It appears that unless the cannabis user decides that the benefits of using are outweighed by the perceived or expected costs, he or she will continue to use.

2.3.4 Conclusion

Cannabis, like other recreational drugs, seems to be used for its perceived positive effects. The evidence from both those with mental health disorders and the general population suggests that using cannabis to manage negative mental states and facilitate social interaction is associated with problems. Both higher frequencies and negative consequences of cannabis use are associated with such use. However, the persistence of cannabis use in these cases speaks strongly for the importance of the positive effects to the user.

2.4 Other risk factors

A recent review of high quality studies assessing the relationship between cannabis and mental health found the following factors to be associated with the onset of cannabis use: being male; prior or concurrent tobacco and alcohol use; having poor parental relationships; and having peers who use cannabis [61]. These factors are all consistent with an Australian study of a large birth cohort [62].

A number of negative outcomes such as poor academic achievement, criminal activity, violent behaviour and conduct disorders are also associated with cannabis and other drug use. Problem Behavior Theory [63] has been one attempt to integrate this broad association of behavioural problems within a framework that emphasises the interaction of the individual and environment rather than simply identifying environmental factors that may influence behaviour. For every example of cannabis use leading to an undesirable outcome, there are typically many similar cases in which such an outcome did not eventuate. Discovering why both sorts of outcomes occur is central to understanding these associations.

Beyond the immediate mental health risks to the user of cannabis, it is also important to consider risks posed through prenatal use of cannabis to the unborn child. A recent systematic review of the neurodevelopmental consequences of prenatal exposure to toxins found that those exposed to cannabis prenatally were at an increased risk of having problems maintaining attention later in life [281]. There is also some evidence that prenatal cannabis exposure is related to experiencing depression and anxiety in childhood and adolescence [282][283]. Other research has found that cannabis use during pregnancy increases the likelihood of cannabis use among offspring at the age of 14 [284]. A recent Australian review in the area pointed out that associations found between prenatal cannabis use and subsequent adverse cognitive, behavioural and psychiatric outcomes may be confounded by unmeasured genetic and environmental factors [285].

3 Psychosis and Schizophrenia

3.1 What is 'psychosis' and how does this relate to schizophrenia?

The term *psychosis* refers to a set of symptoms that impair the ability of a person experiencing psychosis to distinguish reality from fiction. It is characterised by the following signs and symptoms:

- delusions—beliefs that are not consensually validated or demonstrably true;
- hallucinations—perceptions that cannot be verified by others; and
- communication and behaviour that are partly or completely unintelligible.

Psychosis is usually thought of in association with schizophrenia, but is also present to varying degrees in a number of other mental health disorders [30]. It should be noted that discrete psychotic *symptoms* (e.g. seeing something that is not there, as can occur in delirium associated with fever, for example) can be experienced without necessarily being part of a psychotic *disorder*. If the symptoms are severe enough, or there are multiple symptoms co-occurring for a sufficient time, then a psychotic disorder, such as schizophrenia, may be diagnosed (see Box 3.1).

Box 3.1: How is schizophrenia diagnosed?

To diagnose schizophrenia the following criteria need to be met:

(a) Experience of two or more* characteristic symptoms for a significant part of a one-month period:

- delusions (e.g., believing that someone is stealing thoughts from your mind or controlling your actions)
- hallucinations (e.g., hearing a voice commenting on your actions)
- disorganised speech (e.g., incoherent speech, or frequently going off topic in a conversation)
- grossly disorganised or catatonic behaviour (e.g., unpredictable agitation, or strange postures)
- 'negative symptoms', which refer to a set of symptoms such as a lack of emotional expression, lack of speech, and lack of motivation

(b) Social or occupational dysfunction; and

(c) Continuous signs of disturbance for at least six months.

* If the delusion is bizarre, or the hallucination consists of a voice commenting on the person's behaviour or two voices conversing with each other, then only one characteristic symptom is required to fulfil criterion (a).

From the Diagnostic and Statistical Manual of Mental Disorders, fourth edition

Schizophrenia is a psychiatric disorder that can be severely disabling; poor social and occupational functioning is characteristic of the disorder. Schizophrenia can exert a

distressing effect both on the person experiencing this disorder and on their family. It usually emerges in late adolescence or early adulthood and can often persist throughout the person's lifetime, making schizophrenia a significant contributor to the global burden of disease [64]. Approximately one in ten people with schizophrenia will take their own life [30]. It was estimated that $1.85 billion was spent on the direct and indirect costs of schizophrenia in Australia in 2001 [65]. Annual costs have been estimated to be over $46,000 per patient in Australia, with lost productivity accounting for $27,500, inpatient costs accounting for $13,800 and $4,900 in other service costs [66]. In terms of impact on the lives of people experiencing schizophrenia and their family, care, and cost, schizophrenia represents a substantial burden on the community.

3.2 How common is schizophrenia?

There are two main ways to describe the number of people in the population that experience a disorder: prevalence and incidence. Prevalence describes the proportion of people at any one time with the disorder, whereas incidence refers to rate at which new cases of the disorder emerge, e.g. cases per million per year.

Most literature states that the prevalence of schizophrenia is around 1% of the adult population [30]. Males usually have a slightly higher prevalence of schizophrenia than females, as do people born in urban rather than rural areas, and migrant groups versus non-migrants [67][68]. Two recent systematic reviews have found that the median incidence of schizophrenia is 15.2 per 100,000 persons per year [68] and the median lifetime risk of developing the disorder is 0.72% [64]. In Australia, it has been estimated that about 2,000 people are newly diagnosed with schizophrenia every year [69].

It should be noted that the prevalence of schizophrenia is likely to be different among different populations simply because the cause of the disorder is so complex, as will be discussed below [64]. For example, although genes do play a part in the development of schizophrenia, there is also a significant environmental component, which suggests that varying environments would lead to varying levels of psychosis. Indeed, the incidences of schizophrenia in the review mentioned above varied quite widely [70]. It is increasingly acknowledged that the incidence of schizophrenia varies across time and populations [71][70].

3.3 What causes schizophrenia?

The causes, or aetiology, of schizophrenia are elusive. It is likely that a number of risk factors, through a variety of mechanisms, contribute to the development of psychotic disorders [72]. Some examples of risk factors include genes, birth complications, and substance use.

3.3.1 Genes and schizophrenia

With its roots in research conducted in the first half of the 20th century, the genetic influence on the aetiology of schizophrenia is well supported [73]. In the 1930s, it was discovered that the incidence of schizophrenia was about 14% higher within families of someone experiencing schizophrenia than in the general population [74].

One way to estimate the genetic influence of any condition is to compare the concordance of monozygotic (identical) twins, who share 100% of their genes, with that of dizygotic (fraternal) twins, who share 50% of each other's genes on average. That concordance is much higher in identical twins (33% to 78%) than in fraternal twins (8% to 28%) [75]. Adoption studies have revealed that schizophrenia occurs more often in the biological relatives of adoptees experiencing schizophrenia than in the adopted relatives [76]. Having a first-degree relative (i.e., sibling or parent) with schizophrenia is the greatest risk factor for developing the disorder. The particular combination of genes involved in the aetiology of schizophrenia remains unknown, although recent advances have been made [77]. There is clearly a genetic component to schizophrenia, but it is not the only factor contributing to this disorder. If it was, then concordance rates of identical twins would be close to 100%, rather than the most commonly cited rate of 45% [73]. Other factors must also play a role in the development of schizophrenia.

3.3.2 Abnormal brain development and schizophrenia

It has been suggested that schizophrenia may arise from problems that occur around the time of birth, causing the brain to develop abnormally. This is known as the neurodevelopmental theory of schizophrenia [72][78]. For example, maternal malnutrition is recognised as a significant risk factor for schizophrenia [79]. At the onset of schizophrenia, diffuse structural brain abnormalities have been detected, and because this damage does not progress with the disease, it is thought to have occurred prior to the first symptoms of schizophrenia [73]. The particular areas of the brain that usually show abnormalities tend to be slowly developing areas [80]. This could help explain the gap between the damage to the brain and the subsequent symptoms (usually occurring in late adolescence or early adulthood), as abnormalities may not present themselves until the structure to which they relate is fully developed. It has often been noted that certain developmental abnormalities in children, such as social isolation [81], are related to the later emergence of schizophrenia.

Obstetric complications—such as low birth weight and maternal diabetes during pregnancy—have been identified as risk factors for later development of schizophrenia, although the effect sizes are small [82][80]. Other evidence in favour of the neurodevelopmental theory is the observation of childhood developmental abnormalities (such as developmental delays in cognitive and physical abilities)—indicative of abnormal brain development—in children who go on to develop schizophrenia [80]. Other developmental abnormalities in children, such as social isolation [81], may be related to the later emergence of schizophrenia. Although the mechanism of the relationship between brain development and schizophrenia is not fully elucidated, it is well accepted that schizophrenia has a developmental component [80].

3.3.3 Abnormalities in neurotransmitters and schizophrenia

Neurotransmitters are chemicals that transmit signals between neurons, and are a fundamental part of the operation of the brain. The first medications used to treat psychotic symptoms acted principally upon a neurotransmitter known as dopamine. Dopamine is one of many such substances in the brain that mediate communication between its cells [84]. Traditional antipsychotics reduced the activity of dopamine, and also reduced symptoms such as delusions and hallucinations [76]. In contrast, substances that strongly increase

activity of the dopamine system, such as amphetamines, cocaine and L-dopa (used to treat Parkinson's disease), have been shown to worsen symptoms of psychosis or induce them in people who had not experienced psychosis previously [85]. These two pieces of evidence have led to the suggestion that schizophrenia and psychosis arise from a hyperactive dopamine system.

Further research has shown that the relationship between dopamine and schizophrenia is complex; increased dopamine activity has been found in some parts of the brain of people experiencing psychotic disorders, but decreased activity has been found in other parts [86]. It has been argued that the increased dopamine activity is responsible for the so-called 'positive' symptoms of schizophrenia, namely, delusions and hallucinations, while the decreased activity is implicated in the deficits in memory and attention and the 'negative' symptoms such as lack of motivation [87].

The role that other neurotransmitters, such as serotonin or glutamate, play in psychosis and schizophrenia has also received attention over the last few years [76]. It is likely that the relationship between neurotransmitter activity and the psychotic symptoms of schizophrenia is complex [74]. Further research into the biochemistry of schizophrenia, as well as further research into whether the areas of the brain affected in psychosis correspond to the areas of the brain where the neurotransmitter abnormalities are found, will help with the development of antipsychotic medication [76].

The three main hypotheses concerning the aetiology of schizophrenia described so far all have some support. It is likely that all three contribute to the cause of schizophrenia, which may indeed be an interaction between genetics, early brain disturbance, and aberrant neurotransmitter activity [77]. In the last two decades, the importance of environmental or social risk factors, such as substance use, has been clarified [80].

A recent review identifies numerous environmental risk factors related to the incidence of schizophrenia. Included are obstetric complications (discussed in section 3.3.2 above), substance use, stress, immigration, season of birth, urban residence, head injury, viral infection and history of trauma [77]. These risk factors vary in both their influence on schizophrenia and the available evidence for that influence.

3.4 Drug use and psychotic symptoms

Many psychoactive drugs, including alcohol, amphetamine, cocaine and cannabis, stimulate the release of the neurotransmitter dopamine, and increase the risk of experiencing psychotic symptoms, or exacerbate existing symptoms of psychosis [72].

3.4.1 Alcohol

Psychotic symptoms such as delusions or hallucinations can occur either during severe alcohol intoxication or withdrawal from severe alcohol dependence [30]. Individuals who have been diagnosed with schizophrenia are more likely to be dependent on alcohol and to use it in a harmful manner than those without schizophrenia [88], but the reliability of this observation is debated. A cross-sectional survey of the Australian population found that, although alcohol dependence was associated with psychosis, once demographic and other substance use (cannabis use and tobacco use) were controlled for, alcohol dependence

was no longer significantly associated with psychosis [89]. In the British Psychiatric Morbidity Study, alcohol dependence predicted psychotic symptoms in a cross-sectional analysis, even after confounders were taken into account [90], but a follow-up longitudinal study found that heavy alcohol use did not predict psychotic symptoms once confounders were taken into account [91]. In a prospective epidemiological study from the United States, having an alcohol use disorder led to an eight-fold increase in the risk of psychotic experiences among men, regardless of cocaine and cannabis use [92].

It has been found that alcohol can exacerbate some of the symptoms of schizophrenia, such as hallucinations and delusions for a short period of time, but individuals experiencing schizophrenia also report greater euphoria and other positive effects of alcohol than those without schizophrenia [50]. Whether the known disinhibitory effects of alcohol account for this is not clear.

Overall, while transient psychotic signs associated with heavy and prolonged alcohol use are commonly reported, contradictory reports e.g. [93][55] indicate that our understanding of the influence of alcohol on schizophrenia is limited.

3.4.2 Amphetamines

The term ‘amphetamines’ refers to the substances methamphetamine and amphetamine sulphate. The former is currently much more common on the Australian street market [94]. Amphetamines have a variety of street names including base, speed, crystal and ice. Almost 40 years ago, experimental studies showed that the administration of amphetamine to otherwise healthy adults could induce symptoms of psychosis [95][96]. It is now well known that use of amphetamines can induce a psychotic episode that involves experiencing some of the symptoms of schizophrenia, such as persecutory delusions and hallucinations [97]. The psychotic symptoms usually disappear soon after drug use and intoxication cease, although there have been some cases reported where the psychotic episode lasts for longer than one month [98]. Individuals with pre-morbid personality characteristics that are related to schizophrenia (e.g. schizotypal personality traits) have been found to be more likely to develop amphetamine-related psychosis than those who did not have such characteristics [98]. Some argue that abuse of amphetamines sensitises the brain to amphetamine-related psychosis, making it more likely that use of amphetamines will lead to further episodes [99] [100]. There is evidence that levels of dopamine—the major neurotransmitter involved in psychotic symptoms—are elevated in users of amphetamines [101]. This elevated dopamine was associated with more psychotic symptoms, even in the absence of intoxication with amphetamines or other substance use.

It has been suggested that in a small number of cases, amphetamines may have a causal relationship to the development of a chronic psychotic disorder, such as schizophrenia [102]. The relatively low use of amphetamines in the general population may prevent cohort studies from detecting such a relationship. If amphetamines became more widely used, the incidence and prevalence of psychosis would be expected to rise.

3.4.3 Cocaine

Cocaine use has been found to be related to psychotic experiences [103], and a specific cocaine-induced psychosis has been identified, with some studies reporting that about half of dependent cocaine users have experienced this disorder [104]. In an epidemiological study conducted in the United States, daily cocaine use was found to be highly predictive of psychotic experiences [92]. However, once cannabis use and the presence of alcohol disorder was controlled for, the association was no longer significant. This could have been because cannabis or alcohol disorder accounted for the association between cocaine and psychosis, or it could be because there was not enough power to detect the association, since the number of daily cocaine users was very small. The contribution of cocaine to the development of chronic psychotic disorders has received less attention than cannabis, yet there are consistent associations between its use and acute psychosis [105], subsequent psychosis [106][107] and the exacerbation of symptoms in users with psychosis [108].

3.4.4 Hallucinogens

The terms *hallucinogenic* and *psychotomimetic* have been used to describe a number of natural and synthetic substances that produce transient hallucinations and delusions. Individuals who have used hallucinogens typically report awareness of the artificial nature of the drug effects ("insight"), in contrast to psychotic hallucinations which are interpreted as real [109]. However, a small minority of users may fail to do this, and experience psychological and bodily injury as a result [110]. It is generally acknowledged that only heavy use in psychologically unstable individuals is likely to produce chronic psychosis [109].

3.4.5 Nicotine

Tobacco use is widespread among those with schizophrenia. The National Survey of Mental Health and Wellbeing showed that 60% of those who screened positively for psychosis were current tobacco users, compared with 23% of the general population [279]. Nicotine appears to have little or no adverse effects upon psychotic symptoms. It is perceived as having positive effects by those with mental health disorders [111], which may account for it being so commonly used.

It is commonly reported that smoking cigarettes helps those living with schizophrenia alleviate the symptoms of the disorder and the side effects of medication. Experimental studies have supported this by showing that some of the symptoms of schizophrenia (e.g. attentional deficits) are improved with cigarette smoking [112][113]. However, most people with schizophrenia started smoking before their disorder was diagnosed [114] lending some weight to the conjecture that drug use prior to schizophrenia is in part to deal with negative mental states [49]. A cohort study assessed the association between smoking in adolescence and subsequent hospitalisation for schizophrenia, and found a *decreased* risk of schizophrenia associated with heavy smoking [115]. However, the harms of smoking counter any potential benefits, thus the widespread use of tobacco among those experiencing schizophrenia is of concern.

3.5 Life events and schizophrenia

3.5.1 Stress

Animal studies have shown that stress can increase dopamine activity, and stressful adverse life events have been found to precede the onset of psychotic episodes in schizophrenia, although the mechanism of this relationship is not clear [116]. For those with a pre-existing vulnerability to schizophrenia, uncontrollable events and concern about social evaluation may be associated with the initiation or exacerbation of symptoms of schizophrenia [117]. This fits well with the social dysfunction typically observed in individuals diagnosed with schizophrenia, and often in those who eventually develop the disorder [80].

3.5.2 Migrant status

In Europe, increased rates of psychosis and schizophrenia among migrants have been reported [118]. The reason for this is unknown; increased stress associated with moving to another country has been put forward as a possible explanation [118]. Another explanation is the increased stress and disadvantage associated with being a minority group. Recently, Boydell and colleagues [119] found that the incidence of schizophrenia was greater among ethnic minorities in the United Kingdom when they form a smaller proportion of the population. However, Australian studies have not consistently found an association between migrant status and psychosis, with one study reporting decreased rates of psychotic disorders among migrants [120], and another finding that migrants were more likely to endorse psychotic symptoms than individuals born in Australia [121].

3.5.3 Season of birth

Studies from the northern hemisphere have found fairly consistently that individuals with schizophrenia are more likely to have been born in the winter months than at other times of the year [e.g. 122]. The reason for the effect is not clear; some of the possible explanations are viral infections and nutrition, which both vary with the seasons and may lead to pre or neonatal complications, which in turn could lead to the development of schizophrenia [123]. Studies of the effect in the southern hemisphere countries have been less consistent [124]. This season of birth effect has not been as strong in countries closer to the equator with less seasonal variation, which may explain why the effect is weaker in the southern hemisphere countries studied, which tend to have milder winters [124].

3.5.4 Place of birth (urban versus rural)

European studies have shown that those born in urban areas have a higher risk of schizophrenia and psychotic disorders than those born in rural areas [125]. Like the findings on migrant status and schizophrenia, Australian studies have produced conflicting results [120][121]. Reasons for the urban effect could be greater exposure to risk factors such as infections and stress.

3.5.5 Head injury

A history of head injury has long been proposed as a potential risk factor for schizophrenia [77]. Until recently, the studies assessing this link have suffered from methodological problems. Recent studies have produced conflicting findings, with some finding increased risk of schizophrenia in those with a history of head injury [126] and others finding no increased risk [127]. A recent review concluded that, based on current literature, it cannot be stated that head injury plays a causal role in schizophrenia [128].

3.5.6 Trauma

The association between the experience of traumatic events and subsequent development of psychosis has been gaining some attention in the literature lately [77]. A recent longitudinal study found that reporting a lifetime history of trauma (e.g. experiencing physical threats, being in a serious accident, or being sexually abused as a child) at baseline (i.e. the first point of assessment) was associated with reporting psychotic symptoms three years later. This association remained significant once possible confounding factors were taken into account and the effect was stronger for those who were vulnerable to psychosis.

It is clear that a variety of life events are associated with the development of schizophrenia. This review will now examine the evidence that cannabis is an independent risk factor for schizophrenia and, if so, the magnitude of that risk.

4 Cannabis and schizophrenia: What does the research say?

There is consistent evidence from cross-sectional research—meaning research that is undertaken on a group of people at one point in time—that cannabis and psychotic disorders occur together more often than would be expected by chance [129][130][131][132]. Those in treatment for psychosis have high rates of cannabis use and cannabis use disorders (i.e. cannabis abuse and cannabis dependence) [133]. In the general population, individuals diagnosed as having a psychotic disorder have higher rates of cannabis use than those not diagnosed with a psychotic disorder [130][92].

4.1 Why is cannabis suspected of causing psychosis?

Like amphetamines, cocaine and alcohol, the administration of large doses of cannabis (e.g. 60mg of cannabis resin oral) [134] and chronic heavy use [135] have been reported to cause psychotic symptoms lasting several hours in those without an existing psychotic disorder. Experimental trials [136][137] have shown that psychotic symptoms can appear with smaller doses (2.5–5mg intravenous and about 16.5mg oral respectively). These symptoms are temporary and do not persist without further use of cannabis. Early reports of cannabis psychoses that did not resolve did not adequately determine whether the individuals had prior psychotic episodes or risk factors [10].

The typical acute effects of cannabis resemble some of the features of schizophrenia, in particular the sensory distortions, inexplicable mirth, feelings of depersonalisation and loss of motivation. These resemblances have focused attention on the connection between cannabis use and schizophrenia even though the association between tobacco use and schizophrenia is of a similar strength, but without the apparently similar effects.

Similarly, temporary increases in psychotic symptoms after cannabis use are often noted in stable, medicated individuals living with schizophrenia [138][56]. Such transient effects of cannabis must be distinguished from chronic psychoses such as schizophrenia, although differential diagnosis of the acute syndrome may be difficult [139]. One of the reasons why the issue of the relationship between cannabis use and psychosis is so confusing is because of the lack of clear distinction between the association of cannabis use with transient psychotic symptoms, and with chronic disorders (such as schizophrenia) developed later on [10].

4.2 What is needed to investigate the causal association between cannabis use and psychosis?

The evidence of a cross-sectional association between cannabis use and psychosis is not enough to be able to conclude that cannabis causes psychosis. First of all, evidence of association does not provide information about the temporal relationship of the cannabis-psychosis relationship. It remains possible that experiencing psychosis could make it more likely that people go on to use cannabis [140]. Secondly, there may be a third factor that causes both cannabis use and psychosis. For example, the experience of an adverse life event may increase the likelihood of both cannabis use and schizophrenia. One method

of determining whether the cannabis-psychosis relationship is causal is to follow the same group of people (a cohort) over time. Cohort studies allow for the order of onset of cannabis and psychosis to be determined, and other factors that might affect drug use and psychosis to be measured from the outset. Studies with this design ("prospective cohort studies") are reviewed below.

4.3 Major cohort studies: A review of the findings

4.3.1 Swedish Conscript Study

The first longitudinal study to find that cannabis use predicts subsequent development of psychosis was published almost twenty years ago, and was based on a sample of 45,570 male Swedish army conscripts. Conscripts were assessed at age 18 for a number of factors including substance use and psychiatric diagnosis. Hospital records for the next 15 years were examined to determine how many of these conscripts were admitted to hospital for schizophrenia [11].

Although most people treated for schizophrenia during the follow-up period did not use cannabis during adolescence, those who did use cannabis heavily (i.e. more than 50 times before the age of 18) were six times more likely to be hospitalised for schizophrenia by the age of 33 than those who had not used cannabis. Moreover, those who had used cannabis more than ten times (but less than 50 times) were three times more likely to be hospitalised for schizophrenia. However, these represent crude values that do not take confounding factors into account (see Appendix 1 for an explanation of these concepts). Once psychiatric factors, social and family background, and alcohol, tobacco and inhalant use were controlled for, the relative risk associated with being hospitalised for schizophrenia among those who had used cannabis at least ten times was reduced to just over two times and was no longer statistically significant. The adjusted relative risk for those who had used cannabis more than 50 times was not reported (for explanations of relative risks and odds ratios, including the concept of adjustment, see Appendix 1).

It should be noted that psychiatric diagnosis at baseline and having parents that were divorced were better predictors of schizophrenia than cannabis use. It is not possible to determine from the data whether cannabis use preceded psychiatric symptoms, or whether pre-morbid personality traits (i.e. personality traits that preceded cannabis use and development of schizophrenia) were responsible for both cannabis use and the development of schizophrenia.

In addition to the aforementioned limitations, the Swedish conscript study was criticised for not controlling for the use of other potentially psychotogenic (psychosis producing) substances such as amphetamines. A re-analysis of these data, which encompassed a longer follow-up period (27 years as opposed to 15 years), found that cannabis use remained predictive of schizophrenia in a dose-dependent manner even after accounting for other substance use and pre-morbid social integration [15]. Those who had used cannabis at least 50 times by age 18 were about three times more likely to be hospitalised for schizophrenia by the age of 45 than those who had not used cannabis. Overall, these studies showed that cannabis use during adolescence was associated with an increased risk of being hospitalised for schizophrenia over the next 27 years.

4.3.2 Epidemiological Catchment Area (ECA) Study

In the United States of America, a multi-site survey of the population was undertaken between 1980 and 1984 [92]. The Diagnostic Interview Schedule (DIS) was used to measure the presence of psychiatric disorders. This was administered at baseline, and at follow-up one year later. Substance use and social and demographic characteristics were also measured. To assess the risk associated with substance use and psychotic symptoms one year later, those with baseline psychotic symptoms (one or more positive responses to psychotic symptom items on the DIS) were excluded, and 'cases' (i.e. those who experienced at least one psychotic symptom at follow-up) were matched with 'controls' (i.e. those who did not report psychotic experiences at follow-up) on age. The age of the sample ranged between 18 and 49 years. A total of 477 cases were matched with 1,818 controls. Once social and demographic factors (e.g. gender, education, marital status, employment), baseline psychiatric disorders and other substance use (daily cocaine use, alcohol disorder) were controlled for, cannabis use was associated with a two-fold risk of experiencing psychotic symptoms. Put simply, this study suggests that daily cannabis use can double the risk of experiencing symptoms of psychosis.

4.3.3 Netherlands Mental Health Survey and Incidence Study (NEMESIS)

In the Netherlands, a population cohort of 4,045 males and females aged between 18 and 64 years was studied over three years from 1997 to 1999. It was found that those who reported any cannabis use at baseline (year one) were not significantly more likely to experience mild psychotic symptoms at follow-up three years later. However, they were almost 17 times more likely to report clinically significant psychotic symptoms and over 10 times more likely to be judged to need psychiatric care as a result of psychotic symptoms than those who had not used cannabis at baseline [141].

These results were found after controlling for age, sex, socio-economic status and other drug use. Additionally, the effect was dose-dependent, meaning that the higher the level of cannabis use, the greater the risk of experiencing significant psychotic symptoms. Importantly, none of those included in the sample had psychotic symptoms at baseline. Those who did show evidence of psychotic symptoms at baseline were studied separately, and the predictive effect of cannabis on subsequent psychotic symptoms was stronger than for participants who were symptom-free at baseline. This study suggests that cannabis use was associated with subsequent experience of clinically significant psychotic symptoms, and the greater the cannabis use, the stronger the association.

4.3.4 Dunedin Multidisciplinary Health and Development Study

The Dunedin Multidisciplinary Health and Development Study is a birth cohort that has been running in New Zealand since the 1970s. This study assessed childhood psychotic symptoms prior to cannabis use (age 11), cannabis use (defined as having used three times or more) at age 15 and 18, and schizophrenia symptoms and diagnosis of schizophreniform disorder at age 26, among 759 males and females born between 1972 and 1973 [12]. Schizophreniform disorder is similar to schizophrenia in terms of symptoms and signs but lasts for a shorter duration and does not necessarily lead to occupational or social problems [30]. It should be noted though, that the investigators in the Dunedin study used a conservative set of diagnostic criteria for schizophreniform disorder that required social and occupational problems.

Those who had used cannabis by age 15 had more symptoms of schizophrenia than those who had not used cannabis, even once other drug use and childhood psychotic symptoms were controlled for. Cannabis use at age 15, but not 18, was associated with schizophreniform diagnosis. However, this association did not remain significant once childhood psychotic symptoms were controlled for.

A recently published study using the Dunedin birth cohort data found that genetic predisposition moderated the effect of cannabis on psychosis. The gene of interest in this study coded for catechol-O-methyltransferase (COMT). The COMT gene product is involved in the metabolism of dopamine (the neurotransmitter thought to be involved in psychotic symptoms), and has been implicated in studies of the genetic basis of schizophrenia [86]. In the population, there are three allelic variants of this gene: Val/Val Val/Met and Met/Met [142]. It was found that adolescent cannabis users with a particular variant of the COMT gene (Val/Val, 25% of the sample) were at risk of developing schizophreniform disorder by the age of 26, whereas adolescent cannabis users who did not have this variant were not at an increased risk of schizophreniform disorder [86]. Interestingly, Suzuki et al. [143] reported a similar association of vulnerability to the recurrence of methamphetamine psychosis with this allelic variation.

The variants of the genes in and of themselves—that is, irrespective of cannabis use—were not associated with diagnosis of schizophreniform disorder. Moreover, participants with the Val/Val allele who did not start using cannabis until adulthood were not at an increased risk of schizophreniform disorder. The authors argued that this could indicate that the increased risk of psychosis among those with the particular variant of the gene is conditional on the presence of an environmental risk factor (in this case, adolescent cannabis use). The authors suggest that there may be a sensitive period of brain development during adolescence, or that the adult-onset cannabis users had not used cannabis for long enough for the psychotogenic effect of cannabis to take effect.

The significant interaction between adolescent cannabis use and the Val/Val allele remained significant once childhood psychotic symptoms, cannabis use during adulthood, other drug use and conduct disorder were controlled for. Replication of this result is needed before any strong conclusions can be drawn [144], but the data suggest that cannabis use in adolescence may interact with genetic vulnerability to lead to the development of a psychotic disorder. The importance of pre-existing vulnerability to psychosis is also seen in the earlier study [12], which found that there was no association between cannabis use and schizophreniform disorder once childhood psychotic symptoms were controlled for.

4.3.5 Christchurch Health and Development Study

The Christchurch Health and Development Study, another New Zealand birth cohort started in the 1970s, has recently reported results supporting a causal link between cannabis and psychotic symptoms [13]. Ten questions from the Symptom Checklist 90 (SCL-90), which is a measure of general psychiatric distress, were chosen to be representative of psychotic symptoms [145]. These items were administered to the 1,055 participants at age 18, 21 and 25 years to determine psychotic symptoms experienced during the month preceding the interview. This study controlled for a wide variety of possible confounding factors, including prior history of psychotic symptoms and cannabis use, other psychiatric diagnosis (previous

and current), other substance use disorders, adverse life events, deviant peer affiliations, family socio-economic status, family functioning, child abuse, IQ and individual personality characteristics, as well as fixed unmeasured factors—such as genetic factors—which were controlled through statistical modelling. Increasing rates of cannabis use were associated with increasing rates of psychotic symptoms. Daily cannabis users had rates of psychotic symptoms that were between 1.6 and 1.8 times higher (depending on factors controlled for) than non-users of cannabis. The statistical analysis indicated that cannabis use increased the number of reported psychotic symptoms, rather than the other way around.

4.3.6 Early Developmental Stages of Psychopathology Study

The Early Developmental Stages of Psychopathology Study assessed a population-based sample of 2,437 German adolescents and young adults at baseline, and then four years later [14]. Predisposition to psychosis was measured using the SCL-90, and psychosis outcome was defined as at least one (broad psychosis outcome) or two (narrow psychosis outcome) positive responses to the 15 core psychosis items in the composite international diagnostic interview (CIDI). After controlling for age, sex, socio-economic status, childhood trauma, other drug use and predisposition to psychosis, those who used cannabis at least five times at baseline were somewhat more likely to experience any psychotic symptom four years later than those who had not used cannabis. Further analysis indicated that the association occurred in a dose-response manner. The effect was stronger for those who were predisposed to psychosis at baseline than those who lacked such a predisposition. The effect was also stronger for the narrow psychosis outcome than for the broad outcome. Importantly, predisposition to psychosis did not predict cannabis use four years later. Overall, the study suggests that cannabis use among adolescents and young adults who used cannabis were just under two times as likely to experience psychotic symptoms four years later, compared with those who did not use cannabis. The risk was increased for those who used cannabis frequently, and for those who were vulnerable to psychosis.

4.3.7 National Psychiatric Morbidity Survey

In Great Britain a sample representative of the general population were interviewed for the presence of psychiatric disorders using the Clinical Interview Schedule—Revised (CIS-R). Participants who had a mental health disorder or neurotic symptoms at baseline, as well as a random sample of 20% of participants who did not have a mental health disorder were followed up 18 months later [91]. At baseline and follow-up the Psychosis Screening Questionnaire (PSQ) was used to measure psychotic symptoms. Individuals with a psychotic disorder at baseline were excluded from the sample analysed, leaving a sample of 1,795. Cannabis dependence at baseline was related to psychotic symptoms at follow up. However, after sociodemographic variables, drug use and psychiatric morbidity were controlled, neither of the cannabis use variables (used cannabis in the year prior to baseline and baseline dependence on cannabis) were related to psychotic symptoms. Four other variables were related to an elevated risk for psychotic symptoms: living in a rural area, lack of social support, and adverse life events. This study did not find that cannabis use or dependence was related to an increased risk of experiencing psychotic symptoms, among a general population cohort of adults.

Authors (year)	Sample	Cannabis use measure	Outcome (measure)	Controls	Adjusted odds ratio (95% CI)
SYMPTOMS					
Tien and Anthony (1990)	2,295 American adults, aged 18–49	Daily use of cannabis at baseline	Experienced at least one psychotic symptom one year later (DIS)	Psychiatric diagnosis at baseline, age, gender, education, marital status, employment, alcohol use disorder, daily cocaine use, psychotic symptoms at baseline.	2.0 (1.2–3.1) (relative risk)
van Os et al. (2002)	4,104 Dutch males and females from population sample, aged 18–64	Used cannabis at baseline	a) Low-level psychotic symptoms (BPRSa) 3 years later b) Pathological-level symptoms (BPRS)	Age, gender, ethnic group, marital status, education, urban dwelling, discrimination, other drug use. Those with psychotic symptoms at baseline excluded.	a) No significant effect b) 16.9 (3.3–86.1)
Fergusson et al. (2005)	1,055 New Zealander males and females from Christchurch birth cohort	Daily cannabis use in year prior to ages 18, 21, and 25	Psychotic symptoms in past month at age 18, 21 and 25 (SCL-90c)	Other drug dependence, gender, IQ, parental criminality.	1.6 (1.2–2.0)
Henquet et al. (2005)	2,437 German males and females from population sample, aged 14–24	Used cannabis at least 5 times at baseline	Any psychotic symptoms 4 years later (M–CIDId)	Baseline use of other drugs, predisposition to psychosis, age, gender, socioeconomic status, urban dwelling, childhood trauma.	1.7 (1.1–2.5)
Wiles et al. (2006)	1,795 British males and females from the general population	Used cannabis in the year prior to baseline, or dependence on cannabis	Incident psychotic symptoms during the 18 month follow-up period (Psychosis Screening Questionnaire)	Age, gender, area of residence, social support, adverse life events, alcohol and tobacco use, marital status, IQ. Individuals with a psychotic disorder or psychotic symptoms at baseline were excluded.	No significant effect

Authors (year)	Sample	Cannabis use measure	Outcome (measure)	Controls	Adjusted odds ratio (95% CI)
DISORDERS					
Andreasson et al. (1987)	45,570 Swedish male conscripts, aged 18	Used cannabis more that 10 times by age 18	Hospital admission for schizophrenia 15 years later at age 33 (hospital records)	Psychiatric diagnosis at age 18, social & family background, school adjustment, tobacco, alcohol and solvent use.	No significant effect after adjustment
Zammit et al. (2002)	50,053 Swedish male conscripts, aged 18	Used cannabis more than 50 times by age 18	Hospital admission for schizophrenia 27 years later at age 45 (hospital records)	Psychiatric diagnosis at age 18, IQ, social integration, disturbed behaviour, tobacco use, place of upbringing, other drug use.	3.1 (1.7–5.5)
van Os et al. (2002)	4,104 Dutch males and females from population sample, aged 18–64	Used cannabis at baseline	Need for treatment (judged by clinicians)	Age, gender, ethnic group, marital status, education, urban dwelling, discrimination, other drug use. Those with psychotic symptoms at baseline excluded.	10.5 (1.8–63.2)
Arsenault et al. (2002)	759 New Zealander males and females from Dunedin birth cohort	Used cannabis at age 15, continued use at age 18	DSM-IV diagnosis of schizophreniform disorder at age 26 (DIS)	Gender, socioeconomic status, psychotic symptoms prior to cannabis use.	No significant effect
Caspi et al. (2005)	803 New Zealander males and females from Dunedin birth cohort	Used cannabis by age 15 or used regularly at age 18	DSM-IV diagnosis of schizophreniform disorder at age 26 (DIS)	Use of other drugs, childhood psychotic symptoms, IQ, conduct disorder.	10.9 (2.2–54.1) with genetic vulnerability, no association for those without such vulnerability

Abbreviations:

BPRS = Brief Psychiatric Rating Scale

DIS = Diagnostic Interview Schedule

SCL-90 = Symptom Checklist 90

M-CIDI = Munich version of the Composite International Diagnostic Interview

4.4 What do these cohort findings say about the link between cannabis and psychosis?

The cohort studies reviewed here all report associations between cannabis use and subsequent indicators of psychosis, and the association often occurs in a dose-response manner. These results, combined with the cross-sectional evidence for association and biological plausibility, argue that cannabis use, particularly early and frequent cannabis use, is associated with later psychosis. Existing reviews of this issue have concluded that the evidence from these cohort studies show that cannabis use has a causal relationship to psychosis [18][146][147]. However, most of the studies measure psychotic symptoms rather than diagnosed psychotic disorders (see Table 2.1); the latter have more significance clinically. Of the studies that did measure disorders, only one found a relationship between cannabis and hospitalisation for schizophrenia [15]. Whether this can be generalised to the population is uncertain, as an interaction between cannabis use and the stress of military duty on emerging schizophrenia is not implausible [117]. Another found a relationship between cannabis and schizophreniform disorder, but only for those participants with a particular genetic variant [86]. Another found a relationship between cannabis use and the need for treatment associated with psychotic symptoms, but the confidence intervals were imprecise [141]. These and other methodological issues have led to difficulties in definitively stating that cannabis use causes ongoing psychotic disorders. In a recent, comprehensive meta-analysis of the relationship between cannabis and psychosis [148] the authors addressed this issue of psychosis outcome and the relationship persisted. With the application of more stringent statistical methods, it was concluded that heavy cannabis use (e.g. more than 50 uses before the age of 18) was associated with about twice the risk of any psychotic outcome when compared to no use.

4.4.1 Problems with using psychotic symptoms as an outcome measure

A number of important limitations are evident in using psychotic symptoms as a proxy for psychosis. In the Christchurch study, for example, psychotic symptoms were measured using ten items from the SCL-90, from both the 'psychoticism scale' and the 'paranoid ideation' scale. Some studies suggest that the psychosis and paranoid scales of the SCL-90 do not successfully identify psychotic patients in clinical samples, and that participants who are not psychotic may be found to have elevated scores on the psychotic symptom dimension [149]. It has also been argued that this instrument (administered in full) should be used as a global measure of psychological distress rather than a measure of symptoms of particular disorders [150][151]. In the Christchurch study, the average number of symptoms endorsed by daily cannabis users was less than two, and it was unclear whether the particular symptoms measured via the SCL-90 actually measured the cardinal symptoms of serious psychotic disorders (e.g. 'Hearing voices that other people do not hear'), or other symptoms of schizophrenia that are not specific to DSM-IV diagnosis of schizophrenia (e.g. 'Feeling that other people cannot be trusted' or 'The idea that something serious is wrong with your body') [30]. The clinical significance of endorsing one or two symptoms is unclear, particularly when the pattern of symptoms endorsed in those participants who were frequent users of cannabis was not specified [152]. Three other studies, the ECA, EDSP and British Psychiatric Morbidity study, only measured psychotic symptoms; similar limitations apply in terms of determining the clinical significance of these symptoms. It is also possible

that cannabis users, due to familiarity with drug-induced experiences that are similar to psychotic symptoms ("Hearing voices that other people do not hear") and discourse with other users about such symptoms, may be more willing to report them. This may be particularly pertinent for psychotic symptoms that many people experience, but are reluctant to disclose [153][90].

One of the major strengths of the Swedish and Dunedin studies was that the outcome measures—hospital admissions for schizophrenia, and diagnosis of schizophreniform disorder, respectively—were clear and quantifiable in terms of clinical and public health significance. Although the Dutch NEMESIS study measured psychotic symptoms associated with the need for psychiatric care (judged by a panel of professionals), the number of participants who experienced psychosis that warranted treatment was very small (n=7), leading to large confidence intervals.

4.4.2 Reverse causality: The self-medication hypothesis

Cannabis and psychosis may be associated because those who develop a psychotic disorder use cannabis in an attempt to alleviate their symptoms; in other words, to 'self-medicate' [49]. The temporal correspondence between the age at which psychological problems associated with schizophrenia typically appear [154] and the average age of first use of cannabis and other drugs [155] adds to the attractiveness of this model. The prospective design of the longitudinal cohort studies employed specific methods to rule out the self-medication hypotheses, including [13]; exclusion of those with any history of psychotic experiences in the follow-up study [141]; and assessing whether predisposition to psychosis is predicted by later cannabis use [14]. These methods cannot rule out that individuals who are developing a psychotic disorder may use cannabis to alleviate some of the symptoms they experience [156]. Although it is generally accepted that the self-medication hypothesis is not the major explanation for the relationship between cannabis and psychosis [147], it has been reported that schizotypal symptoms precede cannabis use in some cases [157]. A recent Australian study of a group of patients with psychotic disorders found that a bidirectional relationship exists between cannabis use; cannabis use predicted psychotic symptom relapse, and psychotic symptoms predicted cannabis use relapse, independent of medication and other drug use [158]. Overall, while the evidence for self medication of psychotic symptoms with nicotine is substantial, it is considerably weaker for cannabis.

4.4.3 Control of confounding factors

A major strength of both the Christchurch and Dunedin studies is the birth cohort design, which allows for a wide range of early childhood and family risk factors to be measured and controlled for. The Dunedin study was the first study to measure and control for psychotic symptoms in childhood, before the advent of cannabis use. Importantly, the predictive association between adolescent cannabis use and schizophreniform disorder was no longer significant once early psychotic symptoms were controlled for, suggesting that the association between cannabis use and schizophreniform disorder could be explained by existing vulnerability to psychosis. Alternatively, failure to identify a significant relationship may have been due to the small number of participants who were diagnosed with schizophreniform disorder (n=25). Other studies, particularly the ECA, the British survey and

the NEMESIS study, did not measure early childhood and family risk factors as rigorously as the New Zealand studies. The implication of this is that factors that may be related to both cannabis use and psychosis, and may account for the relationship—such as adverse events in childhood—could not be controlled.

Another important variable that is controlled in most, but not all studies, is baseline psychotic symptoms. While the Swedish conscript study assessed psychiatric symptoms and controlled for psychiatric disorders at baseline, it is uncertain whether the psychiatric symptoms recorded were used in the analysis. If this was the case, it would support the conclusion that the limited assessment of social integration satisfactorily controlled for early signs of schizophrenia.

4.4.4 The importance of psychosis vulnerability

Pre-existing vulnerability to psychosis appears to be an important factor that influences the link between cannabis use and psychotic disorders according to the studies reviewed here. The Dunedin data showed that once childhood psychotic symptoms were controlled, cannabis use no longer predicted development of schizophreniform disorder, although the association between cannabis and psychotic *symptoms* persisted [12]. The Dunedin cohort data are also suggestive of a potential genetic vulnerability to the psychotogenic effect of cannabis [86]. However, vulnerability to psychosis has not been measured in many of the studies reviewed here [11][92][91]. Unmeasured vulnerability to psychosis or other unmeasured psychiatric problems may play a role in later cannabis use, and this should be assessed or controlled for in future studies on the relationship between cannabis and psychosis [20]. Other studies (not reviewed here) also support the importance of psychosis vulnerability in the effect of cannabis on psychotic disorders [159].

4.4.5 Measurement of cannabis and other drug use during the follow-up period

A major limitation of the Swedish study was that there was no measure of cannabis use (or other drug use) during the 27-year follow-up period. It remains possible that those who used cannabis at age 18 were more likely to use other psychotogenic (i.e. psychosis inducing) substances such as amphetamines subsequently. This objection is partially answered by the result that amphetamine use at baseline did not affect the relationship between cannabis use and later hospitalisation [15].

4.5 Is the evidence sufficient?

Although the studies reviewed here found a relatively consistent relationship between cannabis and various measures of psychosis, only two of the studies reported a significant relationship between cannabis use and the subsequent development of a psychotic *disorder* meeting diagnostic criteria, once confounding factors were controlled for. The population impact of experiencing one or two *symptoms* of psychosis—particularly when it is often unclear whether the symptoms occurred within the period of cannabis intoxication—is unclear. However, it is obvious that the experience of psychotic symptoms is strongly connected to a subsequent psychosis [80].

In what ways might cannabis influence the development of schizophrenia? The notion that cannabis is sufficient to cause schizophrenia is unlikely to be correct. Even psychotic episodes precipitated by large doses of cannabis almost always resolve with detoxification, and few frequent and/or heavy cannabis users are ever diagnosed with schizophrenia. It seems likely that cannabis interacts with a variety of risk factors, from genetic to personality variables [160], perhaps over some years. In combination with strong risk factors like a genetic predisposition, even modest cannabis or other psychoactive drug use may be sufficient to precipitate schizophrenia. Where the other risks are weaker, a gradual decline to heavy cannabis use related to the known danger of using cannabis to cope with negative mental states and poor social interaction may be more plausible (e.g. [161]). It must be remembered that this applies to other drugs such as alcohol and amphetamines, and especially to polydrug use.

4.5.1 Can cannabis cause schizophrenia that would not have otherwise occurred?

Given the evidence presented above, it is clear that prior cannabis use and schizophrenia co-occur often enough to suggest a causal relationship, and that what we know about schizophrenia and the effects of cannabis are broadly consistent with causal models. Whether another factor is causing both schizophrenia and cannabis use is uncertain. Several studies have presented evidence that prodromal (pre-clinical) symptoms precede both schizophrenia and cannabis use and argue that the effect of these symptoms on cannabis use is sufficient to explain the relationship between such use and eventual schizophrenia. This seems to be the best fit between the causal models presented above and the accumulated evidence. It is still possible that cannabis or other drug use may precipitate schizophrenia in vulnerable individuals who would otherwise have not developed it [162], thus leading to new cases of psychosis.

Despite a rise in the prevalence of cannabis use in the population internationally over the last three decades [2], most studies of the incidence of schizophrenia over that time report either no change [163], or a decrease [164][165] (for a review, see Munk-Jørgensen [166]). It has been generally accepted that the incidence of psychosis and schizophrenia has not changed since the 1970s in Australia [167][1]. If this is the case, then cannabis use may not be causing an increase in psychotic disorders. The fact that the prevalence of cannabis use in Australia is substantially higher than that worldwide should make this effect easier to observe.

However, detecting changes in the incidence of psychiatric disorders is not a straightforward task; increases or decreases may be accounted for by changes in how a disorder is diagnosed, changes in the likelihood of a diagnostic record being available to researchers, or changes in the demographics of the population, such as decreases in the proportion of young people [164]. Indeed, the low incidence of schizophrenia may obscure minor changes in that incidence.

A relatively recent study from the United Kingdom examined the incidence of schizophrenia by assessing hospital admissions in an area of London between 1965 and 1997. Standard diagnostic criteria were applied, and population variations were taken into account [168]. The incidence of schizophrenia increased from 6.8 per 100,000 between 1965 and 1968,

to 15.3 per 100,000 population between 1993 and 1997. This increase in incidence was greater for young people, and occurred mostly in the 1980s and 1990s. A study using the same data found that cannabis use in the year prior to first presentation for psychiatric treatment increased from 1965 to 1999 among all patients [169]. This increase in cannabis use over that period is expected, given general population trends over this time, but the study found that those presenting with schizophrenia had a greater increase in cannabis use than those presenting for other non-psychotic psychiatric problems. Although there were some limitations of this study (e.g. no general population comparison group, no control for confounding factors that may have been related to cannabis use and schizophrenia such as other substance use), the studies are consistent with cannabis use contributing to schizophrenia.

It has been suggested that cannabis use may simply accelerate the onset of schizophrenia [86][170], instead of causing new cases. Age of onset in schizophrenia has become lower over the last three decades [171], and cannabis users have been found to be younger at the onset of the first psychotic episode than those who have not used cannabis [172][114]. This may be of clinical importance as earlier age of onset of schizophrenia is associated with poorer prognosis [172].

In summary, there is no convincing evidence of an increase in the incidence of schizophrenia over the last three decades in Australia. The contentious issue of whether cannabis use can cause serious psychotic disorders that would not otherwise have occurred cannot be conclusively answered, although the available evidence strongly suggests that some such cases have occurred.

4.6 How does cannabis compare to other risk factors for schizophrenia?

4.6.1 Relative strength of risk factors

Genetic factors confer a greater risk of schizophrenia than the environmental factors just discussed, including substance use [77]. Because the exposure to other risk factors in the population is relatively higher (e.g. many more people are exposed to an urban environment than to the inheritance of genes from parents who had been diagnosed schizophrenia) the resulting number of cases of schizophrenia may be larger. Therefore, the population attributable risk (PAR) is larger, as shown in Table 4.2 [125].

As has been outlined in this review, there are numerous risk factors that potentially contribute to the aetiology of psychotic disorders. Most studies have focused on the risk factors associated with schizophrenia. How do they compare with one another? A study of a population-based cohort in Denmark compared the relative risks and population attributable risks associated with a variety of factors related to schizophrenia [125]. The table below presents their findings, along with the odds ratio associated with the risk of schizophrenia for those who used cannabis more than ten times during adolescence from the Swedish Conscript study [15]. Both studies used hospitalisation for schizophrenia as the outcome.

Table 4.2 Risk factors for schizophrenia: Relative Risk and Population Attributable Risk

Risk factor	Relative Risk	Population Attributable Risk (%)
One or both parents with schizophrenia	7.2–46.9	3.8
One or more siblings with schizophrenia	7.0	1.9
Used cannabis more than 50 times by age 18[a]	3.1[b]	8.0
Urban place of birth	2.4	34.6
Season of birth	1.1	10.5

Values from Mortensen et al. (1999), except [a], which is from Zammit et al. (2002)
[b] Odds ratio

Family history of schizophrenia was associated with the greatest relative risk for subsequent hospitalisation for schizophrenia; having a father (RR = 7.2; 95%CI = 5.1–10.2), mother (RR = 9.3; 95%CI = 7.2–11.96) or both parents (RR = 46.9; 95%CI = 17.6–125.3) affected greatly increased the likelihood of schizophrenia in a child [125]. The factor with the smallest relative risk was season of birth (RR: 1.1; 95% CI: 1.06–1.18). However, if a large proportion of the population is exposed to such a risk factor, the number of cases can be substantial [124]. The population attributable risk (PAR) is an estimate of the percentage of cases due to one or more risk factors. Mortensen and colleagues (1999) also calculated the PAR for the risk factors, and found that the factor with the highest PAR was place of birth, accounting for 34.6% of hospitalisations for schizophrenia. Season of birth is now the second most significant risk factor, accounting for 10.5% of hospitalisations, but this is for a location in the Northern Hemisphere. Relatively heavy cannabis use in adolescence was the third most significant risk factor for schizophrenia in terms of both measures.

To apply the criteria for a causal association mentioned above, while cannabis use is associated with a diagnosis of schizophrenia, the association is modest. The temporal precedence of cannabis use in schizophrenia is disputed by some research [157] and the same strand of research provides an alternative mechanism for the association. The argument for cannabis as a causal factor in schizophrenia is strengthened by the similarity of some of its effects to the symptoms of psychosis and the common factors acting in other acute drug-induced psychoses. In contrast, an attempt to distinguish characteristic patterns of symptoms of schizophrenia between cannabis users and non-users was unsuccessful [173].

It should also be noted that PAR values can be misleading, particularly when the outcome may be the result of multiple causes [174], as is the case with schizophrenia [77]. The amount of variation in the reported PAR between studies is considerable, raising questions about the meaningfulness and accuracy of any single figure taken in isolation. For an attributable risk ratio to be valid, the influence of other risk factors (e.g. other drug or alcohol use) must not be affected by the elimination of the risk factor in question (i.e. cannabis use). This may not be the case, as decreasing cannabis use could lead to increased use of alcohol or other drugs. Benichou [174] suggests that a weaker interpretation of attributable risk may be appropriate in such scenarios, such that the PAR represents the proportion of the disease that can be linked, rather than attributed, to the exposure.

4.6.2 How does cannabis compare to other drugs?

As mentioned previously, the use of other recreational drugs often precedes the onset of schizophrenia, particularly when more than one drug is used. As an example, the abuse of amphetamines is known to be associated with emerging psychosis, both acute and chronic [99]. The action of amphetamines upon dopamine activity is well known, and both dopaminergic activity and psychotic symptoms increase in those with schizophrenia when amphetamines are administered [175]. However, the lower prevalence of use of amphetamines (see Figure 2.1) makes it difficult to compare the extent to which that use contributes to schizophrenia compared to cannabis.

4.7 What is the underlying mechanism?

If cannabis use exacerbates psychotic symptoms, or triggers the onset of a psychotic disorder, a plausible biological mechanism would aid the understanding of its effect.

The cannabinoid Δ^9-tetrahydrocannabinol (THC) was characterised in the 1960s, but for the next 20 years, it was unclear how THC exerted its effect on the brain [4]. In 1988, endogenous THC-binding receptors were reported [176]. Soon after, a naturally occurring cannabinoid (termed an 'endogenous cannabinoid', or an 'endocannabinoid') was identified in the brain—anandamide [177]. Since then, several other endocannabinoids have been discovered [4]. It is these discoveries that have made the investigation of how cannabis may be related to psychosis possible.

There are several main lines of evidence suggesting that it is biologically plausible that cannabis is involved in the occurrence of psychotic symptoms. Firstly, high concentrations of cannabinoid receptors (binding sites) in the brain are found in areas of the brain that are thought to be linked to schizophrenia, such as the hippocampus [178][179]. Secondly, cannabis receptors appear to be important in modulating the activity of dopamine, which is thought to be involved in psychosis [180]. Thirdly, the endogenous cannabinoid system may be abnormal in those living with schizophrenia, such that levels of endocannabinoids, like anandamide, are elevated in those with psychotic disorders [181], and this may be a response to psychosis [182]. In contrast, a more recent study [183] has found that frequent cannabis use may reduce this anandamide activity, providing a mechanism for the exacerbation of psychotic symptoms by cannabis. Finally, a gene for a cannabinoid receptor in the brain has been found to be associated with a specific type of schizophrenia [184], although not all studies have found an association [185].

4.8 Conclusion

Evidence implicating cannabis use in the aetiology of schizophrenia has accumulated in the past 20 years. The conflicting nature of this evidence and its restricted generalisability argues for caution in assuming that cannabis use can cause schizophrenia. Nonetheless, there appears to be a sound basis for informing current and potential cannabis users of the potential risks. This applies with even greater force to those individuals with known or suspected vulnerabilities to schizophrenia.

Key points: Cannabis and schizophrenia

There are many factors that contribute to the emergence of psychotic disorders such as schizophrenia.

- There is good evidence that cannabis makes some symptoms of psychosis transiently worse.
- The evidence that the association of cannabis use with emerging psychosis is due to self-medication is not conclusive.
- Cannabis use increases the risk of schizophrenia among those with other risk factors.
- While it is likely that cannabis use leads to cases of schizophrenia that would not have occurred otherwise, the number of such cases is probably small.

5 Depression, bipolar disorder and anxiety

The question of whether cannabis use is causally related to depression, anxiety and other mental health disorders such as bipolar disorder did not initially receive the same level of attention as the association between cannabis and psychosis. However, in recent years a great deal more information about cannabis and mood and anxiety disorders has been acquired.

5.1 What are mood and anxiety disorders and how common are they?

The term 'mood disorders' refers to a group of mental health illnesses characterised by alterations in peoples emotional states. The best known mood disorder is major depressive disorder (MDD). Other mood disorders include: dysthymic disorder (depression that is not as severe, but lasts longer than episodes of MDD); bipolar I disorder (persistent elevated mood—known as a manic episode—usually accompanied by depressive episodes, explained below); bipolar II disorder (depressive episodes and elevated mood that is less extreme than manic episodes); and cyclothymia (depression and mania that are not as severe, but last longer than bipolar I disorder). Disorders such as panic disorder, post-traumatic stress disorder, phobias and generalised anxiety disorder fall under the category of anxiety disorders. Anxiety disorders and mood disorders can often co-occur.

5.1.1 Major Depressive Disorder

The diagnostic criteria for MDD include the experience of one or more major depressive episodes, which are characterised primarily by a sad mood and/or a loss of interest in all things persisting for at least two weeks (see Box 5.1 for the diagnostic criteria) [30]. Age of first onset is typically in the mid-twenties, and most people experience more than one episode in their lifetimes. A depressive episode is distinguished from normal grieving after events such as the death of a loved one by fulfilling certain criteria, such as length of depression, types of symptoms and level of social or occupational dysfunction.

The World Health Organization estimated that depression was the fourth highest contributor to the global burden of disease, and was the second highest in developed countries [186]. About 15% of those with depression will take their own life [187], although there are often other factors involved [188]. MDD affects between 10% and 25% of women and 5% to 12% of men during their lifetimes [30].

Box 5.1: How is depression diagnosed?

To diagnose major depressive disorder, there needs to be at least one major depressive episode. The criteria for major depressive episode are:

(a) At least five symptoms experienced every day or nearly every day over two weeks; one of these symptoms must be depressed mood (1) or loss of interest or pleasure (2):

- depressed mood for most of the day
- greatly reduced interest or pleasure in all, or almost all, activities most of the day
- appetite changes and/or significant weight loss or gain
- increase (hypersomnia) or decrease (insomnia) in sleep
- psychomotor agitation (unable to sit still) or psychomotor retardation (slowed speech and movement)
- loss of energy or fatigue
- feeling excessively guilty or worthless
- inability to concentrate, think or make decisions
- thoughts of death, suicide, or suicide attempts

(b) The symptoms do not meet criteria for a mixed episode (which is elevated mood as well as depressed mood);

(c) Social or occupational dysfunction, or clinically significant distress;

(d) Symptoms are not due to direct effect of drugs or alcohol, or a medical condition; and

(e) Symptoms are not better accounted for by normal grieving for a lost loved one.

From the Diagnostic and Statistical Manual of Mental Disorders, fourth edition [30]

5.1.2 Bipolar Disorder

As depression is typified by excessive and prolonged sadness and/or loss of pleasure or interest, mania is characterised by inexplicable euphoria or irritability. Bipolar I disorder, formerly known as manic depression, is characterised by one or more manic episodes. Usually, the person will have also experienced at least one depressive episode [30]. Manic episodes include decreased need for sleep, talkativeness, inflated self-esteem, 'racing' thoughts, distractibility, harmful risk-taking behaviours, and increased goal-directed activities lasting at least a week. Manic episodes are also accompanied by occupational or social dysfunction and may feature psychotic symptoms and require hospitalisation. The lifetime prevalence of bipolar I disorder is between 0.4% and 1.6%. One in ten people with bipolar I disorder will take their own life [30], but as with depression, other factors are typically involved [189]. It contributes substantially to the global burden of disease, ranking in the top 20 diseases and injuries in developed countries, and just outside the top 20 in the world [186]. Whereas MDD is more common among females than males, the prevalence of bipolar I disorder does not vary with gender [190].

5.1.3 Anxiety Disorders

Mood disorders often co-occur with other mental health disorders, in particular, anxiety disorders. The DSM-IV lists twelve disorders under the category of anxiety disorders, including panic disorder (with or without agoraphobia), social phobia, post-traumatic stress disorder, obsessive–compulsive disorder, specific phobia, and generalised anxiety disorder [30]. They are the most prevalent group of mental health disorders, with most population-based studies finding that approximately one in four people experience an anxiety disorder [191]. In contrast to mood disorders and psychotic disorders, anxiety disorders often first appear in childhood or adolescence. Anxiety disorders are more prevalent among women than men.

5.2 What causes these mental health disorders?

5.2.1 Genes

There are many family and twin studies that have shown that genes passed on by parents and shared with siblings have a strong influence on mood disorders [192]. For example, one twin study of 960 twin pairs found that among identical twins in which one had a mood disorder (either MDD or bipolar I disorder), 70% of the co-twins also had a mood disorder. Among non-identical twins, the concordance rate was 35% [193]. There is some evidence that genes play a greater role in bipolar disorder than in MDD [192]. It is likely that more than one gene influences mood disorders, as is the case in schizophrenia. Anxiety disorders also have a genetic component, with panic disorder having the largest heritability [191]. While genes play an important role in the aetiology of mood and anxiety disorders, there is clearly an environmental component. An inherited predisposition almost certainly requires environmental influences for the disorder to emerge [192].

5.2.2 Abnormalities in brain chemicals

Three different neurotransmitters have been implicated in the underlying cause of depressive symptoms: dopamine, noradrenaline and serotonin [194]. Early models proposed that the activity of these chemicals was depleted, but were unable to explain subsequent observations. Particular patterns of up- and down-regulation, perhaps with temporal variations, may lead to depression [194]. It is likely that anxiety disorders and bipolar disorder have similarly complex neurotransmitter abnormalities underlying them.

5.2.3 Personal and social factors

Stressful events such as divorce or losing a loved one often appear to precipitate both bipolar disorder and MDD [190]. There is a plausible biological mechanism that may underlie this association. It has been found that stress hormones are over-produced in those with depression [195]. Most studies have found that MDD is more common in urban areas than rural areas [190], and this may be related to the increased stress associated with living in the city.

Anxiety disorders may also follow adverse life events, particularly post-traumatic stress disorder (which requires the experience of trauma in the criteria for diagnosis), and phobias [191].

Certain personality traits, such as early sensitivity to anxiety and inhibition of behaviours have been found to be more common among people who develop anxiety disorders [191].

Cross-sectional surveys of the general population in the US and Australia have shown that depression and anxiety are related to drug and alcohol dependence [196][197][198]. Experimental studies have shown that in the short term, alcohol use can cause symptoms of depression [199][200]. There are also prospective studies which show that drinking alcohol is related to subsequent onset of depression (for a review, see [102]). The relationship between substance use and anxiety disorders appears to be bidirectional; anxiety disorders have been found to elevate the risk for substance use disorders, and substance use has been found to trigger anxiety [191].

Both the Epidemiological Catchment Area study [197] and the National Comorbidity Survey [198] found that bipolar disorder was more strongly associated with alcohol and drug dependence than any other major psychiatric disorder. Some studies have reported that substance use usually precedes the onset of bipolar disorder, but it is known that both bipolar disorder and substance abuse are related to the presence of externalising symptoms (conduct disorder) in childhood (for a review, see Levin and Hennessey [201]).

6 Cannabis and depression: What does the research say?

The first medicinal use of cannabis in the Western world was as an antidepressant and there have been case reports of patients with depression that have shown a better response to cannabis than to conventional antidepressants [202][203]. The otherwise counterintuitive report of cannabis also reducing mania [204] is consistent with the hypothesised stabilising influence of the endocannabinoid system [182]. However, heavy cannabis use has been associated with depression [205].

The USA and Australia have conducted national surveys that have assessed the level of various mental health disorders in the population in recent years. In Australia, data from the National Survey of Mental Health and Well-being was used by Degenhardt and colleagues [206] to assess the relationship between depression and cannabis use. A positive relationship was found between cannabis use and depressive disorders, and this relationship became stronger with heavier or more problematic cannabis use. However, once other drug use was controlled for—particularly alcohol and tobacco—the relationship did not remain significant [130]. The authors concluded that there was no direct relationship between cannabis use and depression, but acknowledged that there may be an indirect one such that cannabis users are more likely to be dependent on other drugs, which may in turn increase the risk of depression. As an avoidant coping style, which includes using drugs, is associated with depression [207], this is a plausible explanation.

Agosti and colleagues [129] used the data from the United States National Comorbidity Survey to assess the prevalence of psychiatric disorders among those with cannabis dependence. They found that the vast majority (90%) of cannabis-dependent respondents also had a lifetime mental health disorder, compared to just over half of those without cannabis dependence. Cannabis-dependent respondents were over two times as likely to have ever experienced clinically-significant depression as those who were not dependent on the drug. Furthermore, those who were currently using cannabis were still twice as likely to have a *current* mood disorder as those who had never been dependent on cannabis.

Further analysis of the United States National Comorbidity Survey data showed that, although history of cannabis use and cannabis dependence were associated with an increased risk of experiencing an episode of clinically-significant depression, this risk was moderate and was not greater than the risk of depression associated with being female or a tobacco smoker [208]. Among Canadian adolescents, cannabis use has been found to be an independent risk factor for depression [209]. Risk was analysed in the former study by taking into account the age of first cannabis use and the age of first episode of depression and in the latter study by an instrument designed to measure depression risk. However, these are not ideal methods for evaluating whether cannabis is a causal factor for depression as the studies were cross-sectional.

Prospective studies are required to determine whether there is an association between cannabis and depression and, if so, to assess its causal structure [208]. Until quite recently, there was a lack of prospective cohort studies assessing the relationship between cannabis

and depression, and reviews were unable to make firm statements about the nature of the relationship [205]. In the last few years, a number of studies have been released that assess whether cannabis use predicts depression [18][210][211][62]. These as well as earlier studies are reviewed below.

6.1 Major cohort studies on cannabis and depression: A review of the findings

6.1.1 Christchurch Health and Development Study

Fergusson and Horwood [212] assessed early cannabis use and subsequent psychosocial outcomes among a birth cohort in New Zealand and found that the rates of experiencing an episode of clinically-significant depression between the ages of 16 and 18 years were significantly higher for those that had used cannabis between the ages of 15 and 16 than those who had not used the drug. However, once confounding variables were controlled for, this association was not significant. The variables that were controlled included: coming from a socially disadvantaged background; having adverse experiences in childhood; associating with deviant peers; and having poor parental attachments.

A more recent study of the same birth cohort found that cannabis use was associated with depression, suicidal ideation (i.e. having thoughts of taking one's own life) and attempting to take one's own life, particularly those who used cannabis at least weekly [213]. Weekly cannabis users between the ages of 14 and 15 were at greater risk of suicidal ideation and attempt than weekly cannabis users who were 20 to 21 years of age. The birth cohort design allowed for a variety of confounding factors to be controlled for, including adverse life events, deviant peer affiliations, alcohol abuse, age of leaving school and age of leaving home. After adjusting for these factors, weekly cannabis users at all ages were almost twice as likely to experience depression. Those aged 14 to 15 years were over seven times more likely to have thoughts of ending their life and thirteen times more likely to have attempted to take their own life (confidence intervals were not reported). However, because this particular study was looking at the association between cannabis use and depression/suicide outcome at the same age, it could not be determined whether cannabis use preceded depression, or depression preceded cannabis use.

6.1.2 Epidemiological Catchment Area (EPA) Study

The EPA study is a multisite survey of the adult US population. Participants from one of these sites (Baltimore) were followed up 14–16 years after baseline assessment, to determine whether cannabis abuse predicted later development of depressive symptoms [214]. After adjusting for confounders, it was found that those who abused cannabis at baseline were four times more likely to experience at least one depressive symptom (including thoughts of ending their life and inability to experience pleasure) 14–16 years later. The converse relationship did not exist; depressive symptoms at baseline did not predict follow-up cannabis use.

6.1.3 Children in the Community Study

Another study from the United States followed a community sample of children aged between one and ten years until their late twenties [215]. After control of confounding factors (demographic factors, socioeconomic status and prior episodes of major depressive disorder and substance use disorders) it was found that childhood cannabis use (prior to the age of about 14 years) was associated with a modestly increased risk of MDD in the late twenties, compared to those who had not used cannabis. The association between adolescent cannabis use and later MDD was similar (see Table 6.1). However, the association between cannabis use in the early twenties was not associated with later MDD.

6.1.4 Lives Across Time Study

The Lives Across Time: A Longitudinal Study of Adolescent and Adult Development (LAT) study commenced in 1988 with the aim of measuring the effect of alcohol and cannabis use by adolescents on subsequent functioning by the cohort. Among other measures, cannabis use was measured at four points (15.5 to 17.5 years) near the average age of initiation of cannabis use. Marijuana use trajectories were used to stratify the sample into abstainers, decreasers, experimental users, high-chronics and increasers on the basis of the pattern of use over the two years of adolescent use measured. While increasers (those whose marijuana use increased greatly from 15.5 to 17.5 years) scored higher on the CES-D than abstainers as adolescents, this effect was not significant at the young adult (about 23.5 years) assessment. Notably, increased depression scores were not observed in the high-chronic group at either assessment.

6.1.5 Victorian Adolescent Health Cohort Study

The Victorian Adolescent Health Cohort Study is a cohort study which has been following a group of Australian adolescents since 1992, when they were in Grade 9 or 10 (approximately 14 or 15 years old). Patton and colleagues [216] reported that frequent cannabis use (weekly or more) during adolescence predicted adult depression and anxiety in females, even after controlling for confounding variables such as adolescent depression and anxiety, antisocial behaviour, alcohol use, parental separation and parental education. There was no relationship between depression and anxiety in adolescence and use of cannabis in adulthood. It should be noted that other illicit drug use was not controlled for.

6.1.6 Dunedin multidisciplinary health and development study

A study using data from this New Zealand birth cohort found that late-onset cannabis use (at age 18) was associated with depression at age 26, but early-onset cannabis use (by age 15) was not, once other drug use, gender and socioeconomic status were controlled for [12]. Cannabis use (later or early onset) was not associated with depressive *symptoms*.

6.1.7 National Longitudinal Survey of Youth

The National Longitudinal Survey of Youth is an American longitudinal survey that has been running since 1979. A recent study investigated the association between cannabis use and depression among this cohort once they had reached adulthood [210]. When members of the cohort were assessed in 1994 (when they were aged between 29 and 37 years), the

prevalence of depression was greater among those who had used cannabis during the past year (23%) than those who had not used cannabis (17%). However, after adjusting for a range of potential confounders (age, gender, ethnicity, general health, region of residence, criminal activity, educational achievement, socioeconomic status, depression before cannabis use, and other substance use), cannabis use in the past year was not significantly associated with depression. The researchers also analysed whether heavy cannabis use in the past year was associated with depression, and whether cannabis use in 1998 was associated with depression four years later. The odds ratios associated with these were not significant either. The researchers concluded that associations between cannabis use and depression may be attributable to common factors related to depression and the decision to use cannabis.

6.1.8 National Longitudinal Study of Adolescent Health

This is an American school-based survey that assessed high school students (mean age 15) on a number of variables at baseline and one year later [217]. Although cross-sectional relationships existed at each assessment, after controlling for a number of variables (see table 6.1), there was no relationship between cannabis use at baseline, and depression at follow-up. There was also not a relationship between depression at baseline and cannabis use at follow-up.

6.1.9 Ontario Child Health Study

The Ontario Child Health Study is a prospective study of a cohort of adolescents, aged between 12 and 16 at baseline, followed up after four years and eight years. A very recent study assessed the relationship between adolescent and adult cannabis use, defined as any use in the last six months (adolescence) or 12 months (adulthood), and depression in adulthood, defined as diagnosis of major depressive disorder in the previous 12 months [211]. It was found that those who used cannabis in adolescence, but did not continue to use in adulthood, were not at an increased risk of adult depression, after control of confounding factors assessed in adolescence (socioeconomic status, single parent home, family functioning, gender, age, grade failure, health status, externalising syndromes—such as behavioural problems, and internalising syndromes—such as depression and anxiety). However, those who used cannabis in adulthood but not in adolescence were over twice as likely to experience depression in adulthood, and adult cannabis users who began using cannabis during adolescence were over four times as likely to experience depression.

6.1.10 The Mater University Study of Pregnancy (MUSP)

The Mater University Study of Pregnancy (MUSP) is a birth cohort study commenced in 1981. One aim was to assess the association between cannabis use and anxiety and depression [62]. Anxiety and depression were measured together using the Youth Self-Report questionnaire at the age of 14 and the Young Adult Self-Report version of the Child Behaviour Checklist at the age of 21. Frequency of cannabis use during the past months was assessed at age 21, as well as the age of first use. Participants were considered ‘early onset cannabis users’ if they reported using cannabis at age 14 or younger. It was found that those who used cannabis frequently were about twice as likely to have symptoms of anxiety and depression, and about three times as likely if cannabis use had been

initiated at age 14 or earlier. These associations were found after controlling for a variety of socio-demographic factors, alcohol consumption, smoking and mental health disorders. Additionally, a relationship still existed between cannabis use and anxiety and depression even when no other illicit drugs had been used. No association was found between symptoms of anxiety and depression at age 14 and use of cannabis at age 21.

6.1.11 Cannabis and suicide risk

The studies reviewed so far have mainly focused on depressive symptoms or diagnosis of a major depressive disorder. However, some also assess the relationship between cannabis use and suicidal behaviour. The Christchurch study found that cannabis use was associated with increased risk of thoughts of suicide and attempting suicide, particularly for younger people [213]. Suicidal ideation was one of the depressive symptoms that were predicted by cannabis use in the Epidemiological Catchment Area study from the United States [214]. Another study from the United States assessed risk for suicide among a group of school children (n=1695) in early adolescence, late adolescence and adulthood [218]. Females who began using cannabis in early adolescence were almost three times more likely than females who did not do so to have suicidal thoughts in adulthood. In the National Longitudinal Study of Adolescent Health [219], cannabis use was found to be a risk factor for suicide attempts, but a number of confounding variables were not controlled for, and the follow-up period was short (11 months).

Table 6.1 Cohort studies on cannabis use and depression

Authors (year)	Sample	Cannabis use measure	Outcome (measure)	Controls	Adjusted odds ratio (95% CI)
SYMPTOMS					
Bovasso (2001)	1,920 American males and females from a population cohort	Cannabis abuse at baseline (DISa)	Any depressive symptom (ever) lasting 2 weeks or longer measured at follow-up 14–16 years later (DIS)	Baseline depressive symptoms, age, gender, ethnicity, antisocial symptoms, marital status, educational achievement, household income, stressful life events, physical and mental health, symptoms of psychiatric disorders and other substance use.	4.0 (1.2–13.0)
Fergusson et al. (2002)	1063 New Zealander males and females from Christchurch birth cohort	Cannabis use since previous assessment at age 15 (i), 18 (ii) and 21 (iii)	a) Presence or absence of suicidal thoughts since assessment at age 15, 16, 18 and 21 (self-report) b) Number of suicide attempts since assessment at age 15, 16, 18 and 21 (self-report)	Unmeasured fixed effects, adverse life events, deviant peer affiliations, alcohol use, age of leaving school and age of leaving home.	a) (i) 7.3; (ii) 3.6; (iii) 1.8 b) (i) 13.1; (ii) 3.3; (iii) 0.8 Note: 95% CI not reported
Windle and Wiesner (2004)	829 American young adults from an initial sample of 1216 adolescents	Cannabis use at four occasions from 15.5 years to 17.5 years of age—grouped as five “trajectories” (see p54)	CES-D scores at average age 23.5 years	Adolescent—family support, alcohol use, friends’ use of alcohol/ drugs, educational attainment, stressful life events. Adult—family cohesion, current cannabis and alcohol use, friends’ use of illicit drugs, educational attainment.	No significant relationship of depression scores to cannabis use trajectories

Authors (year)	Sample	Cannabis use measure	Outcome (measure)	Controls	Adjusted odds ratio (95% CI)
Hayatbakhsh et al. (2007)	3,239 Australian males and females from the Mater University Study of Pregnancy birth cohort	Cannabis use retrospectively assessed at age 21 (self-report) Cannabis use was measured for late onset and frequent use (a), early onset and frequent use (b), sole use (c), and use with other substances (d)	Symptoms of anxiety and depression from the past 6 months measured at 14 (YSRb) and 21 (YASRc).	Gender, mother's age and education, maternal marital status and quality, family income, maternal substance use, adolescent mental health, adolescent smoking status and alcohol use.	a) 2.3 (1.5–3.6) b) 3.0 (1.8–5.2) c) 2.1 (1.1–4.0) d) 2.7 (1.8–4.1)
DISORDERS					
Fergusson and Horwood (1997)	935 New Zealander males and females from Christchurch birth cohort	Past year cannabis use at age 16 and cannabis use between age 16 and 18 (CIDId used for latter)	DSM-IV diagnosis of depressive disorder at age18 years (CIDI)	Maternal age, SESe, gender, changes of parents, parental history of offending, childhood sexual abuse, conduct problems, childhood IQ, self-esteem, novelty seeking, mood or anxiety disorder, alcohol abuse, daily smoking, juvenile offending, parental attachment and defiant peer affiliations.	No significant effect
Fergusson et al. (2002)	1063 New Zealander males and females from Christchurch birth cohort	Cannabis use since previous assessment at age 15, 16, 18 and 21	DSM-III-R and DSM-IV diagnosis of depression since previous assessment at age 15, 16, 18 and 21 (CIDI)	Unmeasured fixed effects, adverse life events, deviant peer affiliations, alcohol use, age of leaving school and age of leaving home.	1.7 (weekly cannabis use at all ages) Note: 95% CI not reported

Authors (year)	Sample	Cannabis use measure	Outcome (measure)	Controls	Adjusted odds ratio (95% CI)
Brook et al. (2002)	736 American males and females from a community sample aged 1–10 years at baseline	Frequency of cannabis use retrospectively assessed 22 years later via self-report of use a) 8, b) 11, and c) 17 years after baseline.	DSM-IV diagnosis of MDDf assessed 22 years after baseline (CIDI)	Prior episodes of MDD or substance use disorder, demographic factors, SES, and childhood aggression.	a)1.6 (1.1–2.2) b) 1.4 (1.1–1.9) c) No significant effect
Patton et al. (2002)	1601 Victorian high school students aged 14–15 at baseline	Frequency of cannabis use in the past 6 months during adolescence	Mixed depression and anxiety (CIS-Rg) at age 20–21—not as severe as anxiety or depressive disorders, but clinical intervention still appropriate	Adolescent depression and anxiety, alcohol use, antisocial behaviour, parental separation and parental education.	1.9 (1.1–3.3) for females No significant effect for males
Arsenault et al. (2004)	759 New Zealander males and females from Dunedin birth cohort	a) Use of cannabis by age 15, continued use at age 18 b) Use of cannabis by 18 (no use at 15)	DSM-IVh diagnosis of depression at age 26 (DIS)	Gender, SES and other drug use.	a) No significant effect b) 1.59 (1.01–2.49)
Wade and Pevalin (2005)	4,834 United States school children	Used cannabis in past 30 days (mean age 15)	Depression one year later (CES-D)	Age, gender, delinquency, alcohol and other substance use, SES, area of residence, ethnicity, and family, school and peer attachment.	No significant effect

Authors (year)	Sample	Cannabis use measure	Outcome (measure)	Controls	Adjusted odds ratio (95% CI)
Harder et al. (2006)	8,759 United States males and females from population sample, aged 29–37 in 1994	a) Self-reported past year cannabis use in 1994 b) Self-reported past year cannabis use in 1998	a) Depression in the past week in 1994 (CES-Di) b) Depression in the past week four years later 2002 (CES-D)	Age, race, gender, general health limitations, region of residence, criminal activity, alcohol use, cigarette use, excessive alcohol use, use of hard drugs, depression, educational achievement and SES.	No significant effect after adjustment for a) or b)
Georgiades and Boyle (2007)	1,282 Canadian males and females from a general population sample aged 12–16 years at baseline (1983) or at the first follow-up (1987)	a) Any cannabis use in the past 6 months at age 12–16 (T1) b) Any cannabis use in past year at age 26–34 (T2) c) Any cannabis use at T1 and T2	12 month prevalence of MDD at T2 (CIDI)	Family SES, single parent home, family functioning, gender, age, grade failure, medical condition, health status, externalising and internalising syndrome scales.	a) No significant effect b) 2.6 (1.7–4.0) c) 4.5 (2.0–9.7)

Abbreviations:
DIS = Diagnostic Interview Schedule
YSR = Youth Self-Report
YASR = Young Adult Self-Report version of the Child Behaviour Checklist
CIDI = Composite International Diagnostic Interview
SES = Socioeconomic Status
MDD = Major Depressive Disorder
CIS-R = Computerised Revised Clinical Interview Schedule
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth ed.
CES-D = Centre for Epidemiological Studies—Depression questionnaire

From the results summarised in Table 6.1, the majority suggest that the duration, frequency and intensity of cannabis use all seem directly related to the emergence of depression. If cannabis use is actually causing cases of depression, this indicates both cumulative and dose/response effects. Before accepting this conclusion, two points should be considered. As most studies have used diagnoses of depression rather than reported symptoms, they avoid the problem of extrapolating from the latter to the former. The greater prevalence of depression compared with disorders such as schizophrenia facilitates this. Controlling for reverse causality has generally been accomplished by assessing symptoms of depression. However, it is noteworthy that the study assessing changes in cannabis use more comprehensively [220] found that only increasing use was associated with current, but not later, depression scores.

Cognitive styles have been implicated in the development of depression for some time [221] [222], and have led to much better understanding of these disorders [223]. The ways in which the individual thinks about his or her own characteristics, interpersonal relationships and external events and the ways in which he or she copes with the less desirable aspects of these are strongly associated with the emergence of clinical depression. It is recognised that cognitive style [221] and coping style [224] are both part of the depressive syndrome and often precede the emergence of clinical depression by some time [207]. In particular, the avoidant coping style that predicts poorer prognosis in depression [225] also predicts drug use [226] and poorer drug treatment outcomes [227]. An alternative explanation for the results in Table 6.1 is that maladaptive cognitive and coping styles precede both drug use and depression.

Many of the cannabis-depression studies report any cannabis use, some threshold use, or arbitrary levels of light/heavy use rather than quantity or frequency, obscuring any dose-response relationship. Confounding factors were controlled for comprehensively in some studies (e.g. the Christchurch studies), but not in others (e.g. the studies that assessed adult populations and could therefore not control for early childhood and family factors).

Thus it is unclear whether cannabis causes depression that would not have otherwise occurred, or whether it is triggering it in vulnerable individuals who would have experienced depression anyway. Despite these limitations, the studies shed more light on the relationship between cannabis and depression than had previously been available [205]. Frequent and continued use of cannabis is associated with increased risk of experiencing depressive symptoms or depressive disorder in adulthood.

6.2 Reverse causality: Do mood disorders lead to cannabis use?

Most studies that did assess reverse causality, or the self-medication hypothesis found no evidence to support this [228][214][216][217][229][62]. However, a very recent study has found an association between MDD and later cannabis use and cannabis use disorder [230], and as mentioned earlier, the LAT study found a similar relationship [220]. While these studies do not directly support the cognitive/coping style model, they are consistent with it. While there is better evidence that those with developing mood disorders may use cannabis to manage their symptoms, this seems more important for, and may be limited to, females. However, assuming that depressive symptoms are the best long term predictors of major depression may not be an appropriate way to test this model.

The reported effects of cannabis, particularly temporary euphoria and relief of anxiety, support its use for symptomatic relief. A more speculative suggestion is that the sense of enhanced understanding reported by many cannabis users may counteract the feeling of meaninglessness that often accompanies depression.

The most salient factor in the relationship of mood disorders and cannabis is the association of childhood and adolescent conduct disorders with both bipolar disorder and drug use. Maladaptive coping styles, particularly avoidant or escapist, may facilitate the use of recreational drugs to deal with emerging mood and anxiety disorders.

6.3 How does cannabis compare to other risk factors for depression?

In common with other psychiatric disorders, vulnerability to depression is heritable. A meta-analysis of studies estimated the heritability of major depression at 37% [231], and a more recent twin study, the aggregate estimate was 38% [193]. Interestingly, the latter study found that the estimated heritability in women (42%) was significantly higher than in men (29%), a result also noted in an Australian twin study [232]. The effect of heritability is clearly stronger than that of infrequent cannabis use, with only frequent, long-term users approaching the liability of those with a parent who has experienced MDD.

Apart from the stronger heritability, females are at risk of depression from a higher probability of being sexually abused [233], pregnancy and childbirth [234], miscarriage [235], menopause [236] and a variety of other gender-biased influences [233]. The approximate doubling of the lifetime risk of depression in women is at least in part due to the aggregation of such factors.

Polydrug abuse, in particular with combinations like alcohol and cocaine [237], is a strong risk factor for depression. It is notable that polydrug use may be a better predictor of depression than any single drug [238][239], even with therapeutic drugs [240]. This may underlie the disappearance of some drug effects when controlling for other drug use [206]. Reports of polydrug use commencing after the onset of depression [241] suggest a bidirectional association.

Physical impairment, whether acute or chronic, is commonly accompanied by depression [242]. Overall, the more severe or life-threatening the impairment, the greater the risk of depression.

6.4 What is the mechanism of the relationship?

The widely acknowledged association of maladaptive coping styles with emerging depression provides one plausible mechanism for its association with cannabis use. First, as there is little evidence that cannabis directly exacerbates the symptoms of depression, its use as a temporary euphoriant or mood stabiliser is plausible. An avoidant style of coping includes the tendency to use drugs to deal with stressors rather than recruit effective responses. The similar use of tobacco is consistent with this interpretation [243]. A causal model would predict that subclinical depression is ineffectively managed with cannabis, thus delaying treatment.

Alternatively, cannabis use may gradually enhance the underlying causes of depression, either directly by altering neurochemical activity [244] or affecting cognitive factors such as perceptions of rejection, inferiority or abnormality that arise from the interpersonal and social consequences of cannabis use. Current theories of the aetiology of depression emphasise cognitive style as a crucial part of vulnerability to depression [222][223], and suggest that cognitive style, rather than depressive symptoms, is a better predictor of emerging depression.

7 Cannabis and bipolar disorder: What does the research say?

It has been proposed that there may be an association between cannabis dependence and the manic symptoms of bipolar disorder [245]. Among individuals with cannabis dependence, previous treatment of bipolar disorder was significantly more likely compared to a representative sample of the general population [246]. Cannabis use has been associated with poorer outcome among those with bipolar disorder, with duration of cannabis abuse significantly associated with the duration of mania [247], and remission during hospitalisation for bipolar disorder has been found to be less likely in patients abusing cannabis, even in those without concurrent alcohol abuse [248].

There is a lack of prospective research assessing the relationship between cannabis use and bipolar disorder, possibly due to the lower prevalence of this disorder, which limits the possibility of uncovering significant associations. One study found that mania/hypomania (one phase of bipolar disorder) predicted cannabis use disorders more strongly than cannabis use predicted mania [230] and a recent report found that poorer clinical outcome was associated more strongly with cannabis use disorder that began after, rather than before, the first bipolar episode [249]. However, as mentioned above, childhood and adolescent conduct disorders commonly precede both bipolar disorder and drug use.

8 Cannabis and anxiety: What does the research say?

Just as cannabis is implicated in an increased risk of depression but is also used by some to ameliorate the effects of depression, some cannabis users report that the drug relieves anxiety, although anxiety may be reported as an adverse symptom of cannabis use [205]. Of particular interest is whether cannabis use is associated with the development of anxiety *disorders* (such as panic disorder, obsessive compulsive disorder or generalised anxiety disorder), which can create significant adverse outcomes for those living with such a disorder.

A study analysing data from the United States National Comorbidity Survey shows that respondents who were dependent on cannabis were over two times more likely to have a lifetime diagnosis of generalised anxiety disorder or to have ever had panic disorder [129]. Additionally, those with a lifetime cannabis dependence diagnosis who were currently using cannabis were over twice as likely to have a *current* anxiety disorder than those who had never been dependent on cannabis. In Australia, the prevalence of anxiety disorders is higher among those with cannabis dependence (17%) compared with those who do not use cannabis (5%), according to the National Survey of Mental Health and Well-being [206]. However, this relationship was not significant once confounding factors such as demographics, personality, and other drug use were controlled for, suggesting that an unobserved factor may be responsible.

Panic disorder is one of the rare examples of acute cannabis use precipitating a chronic disorder [250]. These cases were unusual and would probably have been precipitated by another stressor, but the causal linkage was evident. While cannabis dependence appears to be related to the development of panic attacks [230], the evidence for cannabis use alone is mixed [230][251].

Both alcohol and cannabis dependence have been found to develop in those diagnosed with social anxiety disorder independently of other anxiety disorders [252].

Both Degonda and Angst [253] and Tournier et al. [43] found that agoraphobia was related to cannabis use. However, Tournier et al. [43] found no relationship between state anxiety and cannabis use and concluded that cannabis neither produced nor relieved anxiety in their sample.

Generalised anxiety disorder has been found to be a predictor of both alcohol dependence and cannabis abuse [254] although less powerful than conduct disorder.

The only studies located that examined the relationship between obsessive compulsive disorder and cannabis use found no significant relationship [255][230] and social phobia appears more strongly associated with alcohol use [253]. There is almost no research into any causal connection of cannabis use with post-traumatic stress disorder.

As previously emphasised, longitudinal research is needed to establish whether a relationship is causal. Two separate longitudinal studies conducted in New Zealand have not found a relationship between cannabis use and anxiety disorders [276][277]. Similarly, an American prospective study found no association between cannabis use and anxiety disorders [276]. Two Australian studies did find a relationship: the first only for females [216]; and the second study for both sexes [62]. However, it should be pointed out that these two studies measured anxiety and depression together, so it is possible that the depression is accounting for the relationship. Additionally, it may be that the longer follow up periods in the latter studies allowed for the relationship to emerge. Overall, the evidence for the claim that cannabis use causes anxiety disorders later in life is not supported by the limited evidence available.

9 Conclusion

The evidence for a causal link between cannabis and mood and anxiety disorders is not as strong as that for schizophrenia. Not only are the effect sizes relatively smaller, there are several factors such as internalising symptoms, conduct disorders and cognitive style that may explain the association. That said, it is equally plausible that the adverse social and psychological consequences of cannabis use may well contribute to the emergence of these mental health disorders. In terms of drug education, it is quite reasonable to warn potential users of the association of cannabis use with mood and anxiety disorders while acknowledging that causality has not been conclusively demonstrated. Early, frequent and continued cannabis use may increase the risk of experiencing depression in adulthood, especially in females.

The research on anxiety and bipolar disorder is sparse, and results are mixed. Thus, it is difficult to conclude whether or not cannabis use plays a causal role in these disorders at this stage, particularly as alternative explanations have not been disconfirmed.

Genes clearly play an important role in mood and anxiety disorders, and it is likely that they interact with environmental risk factors, such as stress, and perhaps substance use, to bring about the onset of the disorder. Genes may lead to greater sensitivity to environmental risk factors, or they may lead to a greater likelihood of exposure to an environmental risk factor, or a combination of both [257].

Key Points: Cannabis and depression, anxiety and other mental illnesses

- Recent evidence suggests that early, frequent and continued cannabis use increases the risk of experiencing depression in adulthood, although the evidence for early self-medication is stronger for depression.
- There is a lack of evidence suggesting that cannabis plays a causal role in the development of anxiety disorders or bipolar disorder.
- Cannabis appears to adversely influence the symptoms of mood and anxiety disorders in the long term even though it may alleviate them during intoxication.

10 Exploring the link further

10.1 Cannabis and mental health: Trends over time

The available data on cannabis use in Australia suggests that current use is quite stable and lifetime use is rising at a rate that is consistent with about 1 in 15 users ceasing per year. Changes in diagnostic practice over time may be the greatest influence on the apparent changes in incidence of mental health disorders.

10.2 Hospital and treatment data

Hospital presentations for problems related to recreational drug use, including cannabis, have risen in recent years [258][259]. There does not appear to have been a corresponding increase in chronic mental health disorders that can be confidently attributed to cannabis use [167, 205].

10.3 Effect of cannabis on the developing brain

There are several lines of research that might illuminate the influence of cannabis use on the developing brain. One of the simplest is the small but reliable decrease in brain volume seen in schizophrenia [260]. Alcohol is known to cause decreases in brain volume [261] and this effect is additive in those with schizophrenia [262]. Similar volumetric changes have been measured in adolescent cannabis users [263]. However, children who eventually are diagnosed with schizophrenia may exhibit a number of morphological and developmental abnormalities [264].

Disturbances in brain chemistry have also received attention in the literature. The most obvious candidate for such attention is the endocannabinoid system itself, including the major endocannabinoid, anadamide, and the CB_1/CB_2 receptor system. Adult brain function is shaped by the environment during neurodevelopment in childhood and adolescence. As the typical initiation of cannabis use is in the period when these adjustments are proceeding, the observed disturbances of endocannabinoid signalling in schizophrenia [183] combined with the possible role of this system in modulating psychotic symptoms [182] may impair development in this system.

10.4 The potency issue

The potency of cannabis, typically expressed as the percentage of THC, has increased to some extent in overseas studies [265]. Whether this has occurred in Australia is less certain, and there is little evidence for such an increase in New Zealand. As most cannabis smokers titrate their dose by gauging the effect of successive inhalations, this may not affect them. However, if an inexperienced cannabis user, or one who wishes to obtain the maximal intoxication, partakes of unusually high strength material, the received dose may be much higher than expected. This could lead to acute cannabis psychosis or some other adverse reaction that might have more serious consequences. As the average potency increase seems to be in the range of two times, it is noteworthy that different cannabis products, such as leaf and hashish, have always had a difference of about ten times in the proportion of THC. Thus cannabis users have always had the option of using high potency material.

Different methods of raising and processing cannabis can also affect the composition of the final product. The concentration of THC varies in different parts of the plant, decreasing from the flowering parts through the leaves to the stems. THC concentration also varies widely between different varieties of *Cannabis* sp. The proportion of THC and cannabidiol (another psychoactive compound in cannabis) also varies. This is an important aspect of potency, as cannabidiol has been shown to antagonise some effects of THC, in particular the anxiogenic (anxiety producing) and psychotogenic (psychosis producing) effects[280]. Indoor cultivation has become more popular as it reduces the risk of detection, optimises growing conditions and facilitates the raising of single varieties and culling male plants to increase the THC content. Higher concentrations of THC are advantageous in trading cannabis products, as the volume of material traded decreases. This allows the product to be more easily transported without detection. Assertions that higher potency cannabis products are gratuitously produced run counter to the profit orientation of most commercial cannabis producers. Maximising profits and evading detection appear to be more straightforward motives for increasing potency.

10.5 What is the burden of illness and attributable risk?

As discussed above, some studies have attempted to place a figure on the proportion of cases of schizophrenia that can be attributed to cannabis (Table 4.1). These figures varied widely from 8% to over 50%. It is very unlikely that an effect at the upper end of this range would not cause a noticeable increase in the population incidence, unless the affected users form a very small proportion of that population. This implies that only the most problematic use of cannabis might justify the highest estimates. Given the data that is available, what can be said about the population impact of cannabis use on psychosis and schizophrenia?

Degenhardt and colleagues [167] tested some possible hypotheses about the nature of the cannabis and psychosis relationship. They tested the hypotheses that a) cannabis causes psychosis that otherwise would not occur, and b) that cannabis precipitates, or triggers, psychosis in those vulnerable, and does not lead to new cases of schizophrenia. Based on existing data, they concluded that the latter is plausible, but the former is not. They found that the latter is consistent with the decreasing age of onset of schizophrenia that has been observed by other researchers [171].

As discussed previously, due to a lack of research on changes in prevalence and incidence of schizophrenia over time, and how this relates to cannabis use, it is difficult to determine what the population impact of cannabis use is in terms of schizophrenia. A recent study used statistical models to project the impact that increases in cannabis use would have on incidence and prevalence of schizophrenia [266]. They made the assumption that cannabis was causally related to schizophrenia, based on the Swedish conscript study (as this study is the only cohort study with schizophrenia as an outcome), and on meta-analyses, which concluded that cannabis use increases the risk of psychosis by approximately two [18][267]. Hickman and colleagues [266] concluded that, if cannabis use does cause schizophrenia, then increases in the disorder should be observable within the next five years, with up to one-quarter of cases of schizophrenia being attributable to cannabis. Caution should be applied when interpreting this study. It is based primarily on only one study of the association between cannabis and schizophrenia, and assumes that all other causes of schizophrenia (of which there are many, some as yet unknown) remain stable.

10.6 Conclusion

Thus far, there is little indication of increases in the incidence of mental health problems that are attributable to cannabis use. This may reflect the fact that only frequent, heavy cannabis use has been strongly linked to such problems. The prevalence of at least yearly cannabis use in Australia has been stable for the past twenty years with minimal changes in the incidence of mental health problems. Similarly, the considerable increase of cannabis use in the previous thirty years was not accompanied by a corresponding increase in mental illness. As with other drugs like alcohol, most cannabis users do not seem to experience serious or enduring problems from the drug. That a small proportion of users do progress to problem use is clear, but the reasons for this, and therefore the ability to identify such persons and minimise the harm they suffer, is not apparent. How to acquire that ability is the present challenge.

11 Summary and Conclusion

11.1 What are the important messages?

In light of the research reviewed above, what should be done to help inform the community about the risks? What evidence-based factual messages can be used to help prevent the adverse mental health effects of cannabis?

Although there is still some uncertainty about the nature of the relationship between cannabis use and mental health disorders, the following conclusions can be drawn:

1. The evidence that cannabis use causes psychotic disorders that would not have occurred otherwise is not conclusive, yet there is good evidence that cannabis use will contribute to the development of psychosis in predisposed people who would have become psychotic anyway and can exacerbate existing psychotic disorders. Those who have a psychotic disorder, and their families, need to be informed of this and be advised to avoid or cease use. It is possible that in a small number of cases, cannabis can cause psychotic disorders in those who would not have otherwise developed psychosis. A precautionary approach would be to inform the public of this possibility.

2. The association between cannabis use and later experience of psychosis (either symptoms or disorders) is stronger for those who are younger when they start using cannabis and who use heavily. Young people should be advised of the potential risk of all of the adverse outcomes of cannabis use, including but not restricted to the possibility that cannabis use may contribute to eventual mental health disorders.

3. Other adverse outcomes associated with cannabis, such as poorer educational achievement and employment, are also more likely the younger the person is when they begin to use cannabis, but the causal role of cannabis use in educational underachievement is not clear.

4. There is some evidence that cannabis use is associated with an increased risk of depression, particularly with long-term, frequent use and early initiation of use. These risks may be greater for females.

5. The use of many psychoactive substances is likely to have adverse effects on those experiencing a mental health disorder.

6. It is unlikely that eliminating the supply of cannabis, if this could be accomplished, would eradicate the motivation to use it. Most cannabis users report that they would substitute another drug, usually alcohol, in its absence.

11.2 Increasing community awareness of the link between cannabis and mental health

Cannabis is but one factor among many that appears to affect the development of mental illnesses. For a small minority of people, it may be a dominant factor, and this is perhaps the most crucial aspect of the message to be imparted to the public. Mental health professionals are extremely limited in their ability to identify these susceptible individuals, and the individuals themselves currently appear to have no greater success. Providing the best information about the pathological interactions between cannabis and psychological states may allow individuals to better assess their own risk profile. For example, it is known that relying upon cannabis to manage negative mood is highly predictive of dependence and the emergence of serious mental illness. Therefore, warnings about not using cannabis to manage stress become important.

11.3 Treatment issues

There is another important point that emerges from this monograph. Although the nature of the relationship between a specific mental health disorder and a particular substance is not always clear from the research available today, what cannot be denied is that mental health disorders and substance use disorders often occur together. Interventions need to be in place to assist those with both types of disorders, as evidence suggests that those with substance use and mental health disorders have worse prognosis than those with only one type of disorder. This point was made clearly in the recent Mental Health Council of Australia report on cannabis and mental illness [268].

Preventing and treating comorbid mental health and substance use disorders is difficult for a number of reasons, including the major issue of which disorder to treat first. The causal relationship between substance use and mental health, as has been explored in this monograph, are complex, and it is not always clear whether one disorder is a consequence or a cause of the other, or if the causal relationships between the two disorders shift and change over time. As pointed out by Steinberg and colleagues [269], when developing treatment for cannabis and mental health disorders, it is likely that a number of interventions will be needed, rather than just a single intervention. Recent research in Australia has been investigating the efficacy of cognitive behavioural therapy as a treatment for people with comorbid psychotic disorders and substance use disorders [270][271], but there is still much research to be conducted in the area of efficacious, effective and cost-effective treatments for comorbid cannabis and mental health disorders [272].

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Appendix 1: A note about reporting association in cohort studies

In section 2.4.1, the major cohort studies addressing the association between cannabis use and psychosis are reviewed. These studies all report the 'odds ratio' when discussing results. This box provides information on how to make sense of these statistics.

Odds ratios and relative risks

The odds ratio (OR) or relative risk (RR) are often used as measures of whether exposure to a certain factor (e.g. smoking) increases the risk of suffering from a certain outcome (e.g. lung cancer), relative to those who are not exposed to the factor [273]. For example, the relative risk of incurring lung cancer among those who smoke has been reported to be 11.34 [274]. Put another way, those who smoke are over eleven times more likely to suffer from lung cancer than those who do not smoke.

Both measures are ratios, which mean that if the OR or RR is reported to be 1.0, then there is no increased or decreased risk of the outcome associated with the exposure. This is because an OR or RR of 1.0 means that the measured outcome is only one time more likely to occur, meaning the likelihood of an outcome is exactly the same. Anything less than 1.0 would mean that the exposure is associated with a decreased risk, and anything greater than 1.0 means the exposure is associated with an increased risk [275].

Confidence intervals

The 95% confidence interval (CI) of an odds ratio will often be reported. The CI gives a range of values around the given OR where the population (or 'true') OR is expected to be located (with 95% certainty). Each CI therefore has an upper and a lower limit, with the OR falling somewhere in between.

For example, if the OR is 1.83, and the 95% CI is 1.44–2.33, this suggests that in 95% of cases, the population OR (the 'true' OR) will fall somewhere between 1.44 and 2.33. This OR is significant. If the range of values included in the CI includes 1.0, then the OR is not statistically significant [275]. For example, if the OR is 1.42, and the 95% CI is 0.51–3.94, then the OR is not significant. The lower limit of the CI means that the risk of the exposure is halved, while the upper limit suggests that the risk is almost quadrupled. No conclusions can be drawn about the risk, if the true OR could be located in such a wide range of values.

Crude and adjusted odds ratios

As mentioned above in section 2.4, an association between an exposure and an outcome may be due to the exposure causing the outcome, or it may be due to confounding factors (e.g., factors that leads to both the exposure and the outcome). Cohort studies that measure a number of these potential confounders are able to assess the relationship between the exposure and the outcome, while controlling for these factors. The odds ratios reported that do not take into account confounding factors are known as 'crude odds ratios' and the odds ratios reported from analyses that have controlled for these factors are known as 'adjusted odds ratios'. The adjusted odds ratios will provide a more accurate picture of the association than the crude odds ratios.