CHANCE, RISK OR CAUSATION? AN OVERVIEW OF THE REVIEWS ADDRESSING THE COMPLEX RELATION BETWEEN CANNABIS AND PSYCHOSIS

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Abstract

Objectives: The debate on the association between cannabis use and development of psychosis is still. It is important to establish if the association is causal and to estimate the magnitude of this effect, as cannabis might represent a potentially modifiable risk factor. This paper aims to review the secondary literature published so far on the association between cannabis use and psychosis in order to summarise their major findings.

Materials and methods: Peer-reviewed literature addressing the effect of cannabis use on the development of psychosis published between January 2000 and August 2016 was searched in the MEDLINE. The search was filtered by language (English) and type of publication (review).

Results: Most of the reviews consistently report a significant association between cannabis use and psychosis, which could be indicative of a causal relationship. People using cannabis have at least a two-fold risk of developing psychosis compared to people who do not use it. The risk is increased in people with genetic/biological vulnerability, if the exposure to cannabis starts early in adolescence and in case of heavy cannabis use (or use of high potency cannabis). The reviewed studies also indicate that cannabis by itself it is neither a sufficient nor a necessary cause of psychosis.

Conclusions: There is an ethical imperative to inform young individuals of the probable mental health risks of cannabis use, including the risk of developing psychosis. The clearest policy implication is that cannabis use should be discouraged among young people and people with high vulnerability to psychosis.

Key words: cannabis, marijuana, psychosis, schizophrenia, genetic predisposition, adolescence, policy

Introduction

Recreational cannabis use has become almost as common as tobacco use among adolescents and young adults, as a culturally acceptable lifestyle choice [1]. In parallel, national legislations and public attitudes toward the use of cannabis are becoming more favourable to cannabis in many countries. In the USA twenty-three states have currently medical marijuana laws and four of these states (Alaska, Colorado, Oregon and Washington) have also legalized marijuana for recreational use. More people are now in favour of legalization of cannabis use than in previous years [2 3] and fewer people around the world tend to see cannabis use as risky [4-6]. No wonder that recreational cannabis use has spread globally to both developed and low- and middle-income countries [7].

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The most recent World Drug report [8] estimates that 360 million people aged 15-64 years, equivalent to 7.6% of the world adult population, use cannabis each year. The corresponding estimates for 2005 were 160 million cannabis users, 4% of the world's adult population [9]. Cannabis use is steadily increasing in West and Central Africa and continues to be high in Western and Central Europe and Oceania, as well as in North America. In the USA cannabis is the most commonly used illicit substance, with 8.4% of the adult population having used cannabis in the past 12 months, and over 22 million people who report smoking on a regular basis; the percentage of users rises to 19.6% for young adults (18-25 yrs) [10]. Similarly, cannabis is the illicit drug most commonly used by all age groups in the EU countries: an estimated 19.3 million Europeans (aged 15-64), or 5.7%, used cannabis in the past 12 months, with 14.6 million of those aged 15-34 (11.7% of this age group) [11].
In parallel, over the recent years the number of people requiring treatment for cannabis use has steadily increased [8]. A substantial body of evidence is currently available showing that cannabis use is associated with a wide range of adverse health and psychosocial outcomes, including development of cannabis use disorders or cannabis dependence, increased risks of motor vehicle accidents, use of other illicit drugs, cognitive impairment, lower levels of educational attainment and psychotic symptoms [12 13].
This latter issue poses particular concerns on a public health perspective. Epidemiologic evidence has accumulated over the last thirty years suggesting that cannabis use may be an important environmental risk factor for developing schizophrenia and related psychoses. With this regard, the pioneering study of Andreasson et al. [14] based on a 15-year follow-up of Swedish military conscripts found that heavy cannabis use was associated with a 6-fold increase in risk for schizophrenia. Debate has since ensued over whether this association is causal. A number of subsequent cohort studies [15-22] replicated Andreasson's findings showing that cannabis use increases the risk of psychosis with a dose dependent relationship and that this association is independent of other clinical and personal characteristics.
However the debate on this issue is still contentious, as researchers involved in the field do not seem to have reached a general consensus [1 12 13 23]. The number of scientific papers addressing the association between cannabis use and psychosis has dramatically increased over the past thirty years, but findings are still conflicting. Such inconsistencies pose considerable problems when it comes to interpreting findings in order to inform decisions to be taken: it is important, in fact, to establish whether the association between cannabis and psychotic disorders is causal and to accurately estimate the magnitude of this effect, as cannabis use might represent a potentially modifiable risk factor for psychosis.
This paper aims to review the secondary literature published so far on the association between cannabis use and psychosis (i.e., narrative reviews, systematic reviews and meta-analyses) in order to summarise their major findings. An early overview of systematic reviews on cannabis and psychosis was published some years ago [24]. However, this paper reviewed studies published up to 2007 and only included systematic reviews. Since this publication, several other primary and secondary research studies addressing the complex issue on relationship between cannabis and psychosis have been published; this indicates the need to update knowledge accumulated on the topic over the last ten years.

Methods

Search strategy

Peer-reviewed literature addressing the effect of cannabis use on the development of psychosis published between January 2000 and August 2016 was searched in the MEDLINE database, using terms from the United States National Library of Medicine thesaurus (Medical Subject Headings, MeSH) when available, with descriptors and Boolean operators (AND/OR) clearly defined. The following MeSH terms were included: ['Substance-related disorders' OR 'cannabis' OR 'marihuana' OR 'marijuana'] AND ['psychosis' OR 'psychotic disorders' OR 'schizophrenia' OR 'psychotic'*]. The search was filtered by species (human), language (English) and type of publication (review). The reference lists of all included reviews were also searched and a citation search of those papers which cited studies included in the review was also carried out.
Titles and abstracts and then full texts were screened to identify relevant reviews for inclusion. Only reviews (both systematic and narrative) that clearly state their objective and define the inclusion criteria were included in this study.

Results

Overall, 110 reports were identified; 62 were excluded on the basis of the title and abstract because they

were not pertinent to the objective of our review, and the full text of 50 articles was retrieved for more detailed evaluation; 8 articles were excluded because they did not fulfil the inclusion criteria. Thus, 42 article (4 systematic reviews and meta-analysis; 6 systematic reviews; 3 narrative reviews and meta-analysis; 29 narrative reviews) were finally included in the present study. More specifically, 38 reviews (both systematic and narrative) addressed the effect of cannabis use in the onset of psychosis, whereas three systematic reviews explored the effect of cannabis on transition to psychosis in clinical high risk populations

Systematic reviews and meta-analyses on the effect of cannabis on the onset of psychosis

Systematic reviews exploring the role of cannabis use on the development of psychosis together with narrative reviews which performed meta-analysis are summarized in Table I.

Seven of the 10 included reviews [25-31] explored the association between cannabis exposure and the occurrence of schizophrenia (any type), schizophrenia-like disorders, psychosis not otherwise specified, or psychotic symptoms; one review [32] assessed the association between any illicit drug use and the occurrence of any psychological or social harm, but it also included studies assessing the association between cannabis use and psychosis considered as 'psychological or social harm'; one review [28] assessed the relationship between cannabis use and affective disorders (depression, suicidal ideation or attempt, anxiety); finally, one review [33] addressed the methodological strengths and limitations of the primary cohort studies which explored the link between cannabis and psychosis, and considered research findings against criteria for causal inference, whereas another article [24] was an overview of published systematic reviews on the association between cannabis use and psychosis which assessed their methodological quality and analyzed the possible reasons for the discordant results.

Seven reviews [25-31] also performed a meta-analysis providing estimates for the risk of psychosis linked to cannabis use. They were concordant in finding an association between cannabis use and the occurrence of psychotic disorders, with an increased risk of developing psychotic symptoms or psychotic disorders in subjects who use cannabis as opposed to nonusers.

Table II shows the study design and the reference of each primary study included in the seven systematic reviews/meta-analyses providing estimates for the risk of psychosis linked to cannabis use.

Overall, 20 longitudinal cohort studies [14-20 34-44] and 8 cross-sectional studies [45-52] were included in the seven reviews. Five of the reviews [25 26 28 30 32] included only longitudinal cohort studies, whereas the other three [27 29 31] included both cross-sectional and longitudinal cohort studies. Two primary studies [19 20] were consistently included in all the seven reviews considered in Table II, one primary study [18] was included in six reviews, and two primary studies [23 38] were included in five reviews.

The first review providing an estimate of the association between cannabis and the subsequent development of psychosis was published by Arsenault et al. [25] The study included five cohort population based studies [14 18-20 23] and found that cannabis use confers an overall twofold increase in the relative risk for schizophrenia (pooled OR: 2.34; 95%CI 1.69 to 2.95) after adjusting for nearly thirteen possible confounders. The authors, while suggesting caution in interpreting their findings, concluded that about 8% of schizophrenia cases could be prevented by eliminating cannabis use in the population. In order to further investigate the consistency of association between cannabis and psychosis and estimate the overall effect size, Henquet et al. [26] carried out a meta-analysis from seven prospective studies [17-20 23 35 38]. In spite of differences in definition (some studies focused on the narrow outcome of schizophrenia, and others focused on the wider outcome of psychotic symptoms) and other differences among studies such as length of follow-up, the authors concluded that cannabis use increases the risk for psychosis (OR: 2.1, 95% CI: 1.7 to 2.5); this finding held regardless of whether it was considered only studies using the narrow clinical outcome (OR: 2.37, 95% CI: 1.7 to 3.3) or the broad outcome of psychotic symptoms (OR: 1.9, 95%CI 1.5 to 2.5). Semple et al. [27] reviewed five cohort [14 15 18-20] and 5 cross-sectional studies [45-49] looking at the association between cannabis and psychosis and found that cannabis is an independent risk factor for psychosis (pooled OR: 2.93, 95%CI 2.36 to 3.64). However, in the light of its major limitations (eg, inclusion of cross-sectional and longitudinal data, use of unadjusted estimates in the meta-analysis and combining effects for 'ever use' of cannabis with those for dependence), the authors concluded that the question of whether cannabis is a precipitating factor in vulnerable individuals or a causative agent remain unanswered. One of the most methodologically sound study was published by Moore et al. [28] who reviewed eleven studies drawn from five adult population-based cohorts [14 16 18 19 36 38 41] and two birth

Table I. Systematic reviews or narrative reviews with meta-analysis exploring the role of cannabis on the development of psychosis.

Author(s)	Year	Aim (s)	Type of paper
Arseneault et al. [25]	2004	To examine the evidence that cannabis causes psychosis by using established criteria of causality	Narrative review and meta-analysis
Macleod et al. [32]	2004	To review general population longitudinal studies relating illicit drug use by young people to subsequent psychological and social harm	Systematic review
Henquet et al. [26]	2005	To investigate the overall effect size and consistency of the association between cannabis and psychosis	Narrative review and meta-analysis
Semple et al. [27]	2005	To review case-control studies that clearly examined the association between cannabis use and schizophrenia or schizophrenia-like psychosis	Systematic review and meta-analysis
Moore et al. [28]	2007	To review longitudinal studies of cannabis use and subsequent psychotic outcomes, and to assess the strength of evidence that cannabis use and these outcomes are causally related	Systematic review and meta-analysis
Ben Amar and Potvin [29]	2007	To review current available data on relationship between cannabis and psychosis	Systematic review
Minozzi et al. [24]	2010	To summarize the findings of systematic reviews on the association between cannabis use and psychosis	Systematic review
McLaren et al. [33]	2010	To review methodological strengths and limitations of cohort studies which explored the link between cannabis and psychosis, and consider research findings against criteria for causal inference	Systematic review
Gage et al. [30]	2016	To review literature exploring the association between cannabis and psychosis	Narrative review and meta-analysis
Marconi et al. [31]	2016	To review studies investigating the association between cannabis use and psychosis and to quantify the magnitude of effect	Systematic review and meta-analysis

Study population	No. of studies	Time frame	Main findings
Adults	4 cohort studies, 1 longitudinal population-based study	n.s.	On an individual level, cannabis increase in the risk for schizophrenia (pooled OR: 2.34; 95%CI 1.69 to 2.95). At the population level, elimination of cannabis would reduce the incidence of schizophrenia by 8%
Adolescents	48 studies	Up to 2003	Inconsistent associations were found between cannabis use and both psychological health problems in adolescents (OR not reported). All these associations seemed to be explicable in terms of non-causal mechanisms
Adults	3 population-based, 1 conscript cohort and 3 birth cohort studies	n.s.	Cannabis is an independent risk factor for psychosis (pooled OR: 2.1, 95%CI 1.7 to 2.5) and could not be explained by confounding or reverse causality. Cannabis is a component cause in the development of psychosis, in which mechanisms of gene-environment interaction are most likely to explain this association
Adults and adolescents	4 cohort and 7 cross-sectional studies	Up to 2004	Cannabis is an independent risk factor for psychosis (pooled OR: 2.93, 95%CI 2.36 to 3.64). However, the question of whether cannabis is a precipitating or a causative factor in the development of schizophrenia remains
Adults	5 adult population-based cohorts and 2 birth cohort studies	Up to 2006	Cannabis use increases the risk of developing psychosis in people who had ever used cannabis (pooled OR: 1.41, 95%CI 1.20 to 1.65), with greater risk in those who used cannabis most frequently (OR: 2.09, 95%CI 1.54 to 2.84). At the population level, elimination of cannabis would reduce the incidence of any psychotic outcome by 14%
Adults	10 cohort studies	Up to 2005	Cannabis increases the risk of developing psychosis among vulnerable individuals and can negatively affect the course of preexisting chronic psychosis. This conclusion should be tempered by uncertainty arising from a series of methodological issues including the assessment of cannabis use, measurement of psychosis, reverse causality and control of other confounders
Adults	5 systematic reviews	Up to 2007	A consistent association between cannabis use and psychosis was found in the published reviews, though it is not possible to draw firm conclusions about a causal relationship
Adults	10 cohort studies	Up to 2008	Criteria for causal association between cannabis and psychosis are supported by the review. However, the issue of whether cannabis use can cause psychotic disorders that would not otherwise have occurred cannot be answered from the existing data
Adults and adolescents	10 cohort studies	n.s.	Cannabis increases the risk of developing psychosis (pooled OR: 1.46; 95%CI 5 1.24 to 1.72). Further studies are required to determine the magnitude of the effect, the effect of different strains of cannabis on risk, and to identify high-risk groups particularly susceptible to the effects of cannabis
Adults	6 cohort and 4 cross-sectional studies	Up to 2103	Cannabis use increases the risk of psychosis (OR: 1.97, 95%CI 1.68 to 2.31); a dose-response relationship between the level of use and the risk for psychosis was also found, since the risk doubled for heavy users (OR: 3.90, 95%CI 2.84 to 5.34)

Table II. Primary studies included in the systematic reviews/meta-analyses providing estimates for the risk of psychosis linked to cannabis use.

	Marconi et al. 2016	Gage et al. 2016	Moore et al. 2007	Ben Amar & Potvin, 2007	Henquet et al. 2005	Semple et al. 05	Arseneault et al. 2004
Cohort studies							
Andreasson et al., 1987 (Swedish conscript cohort) [14]			x			x	x
Andreasson et al., 1989 (Swedish conscript cohort) [15]						x	
Tien & Anthony, 1990 (ECA) [16]	x	x	x				
Weiser et al., 2002 [17]					x		
van Os et al., 2002 (NEMESIS) [18]		x	x	x	x	x	x
Zammit et al., 2002 (Swedish conscript cohort) [19]	x	x	x	x	x	x	x
Arseneault et al., 2002 (Dunedin birth cohort study) [20]	x	x	x	x	x	x	x
Philips et al., 2002 [22]				x			
Fergusson et al., 2003 (CHDS) [23]		x	x	x	x		x
Degenhardt et al., 2003 [34]				x			
Stefanis et al., 2004 [35]					x		
Zammit et al., 2004 (Swedish conscript cohort) [36]			x				
Caspi et al., 2005 (Dunedin birth cohort study) [37]			x				
Henquet et al., 2005 (EDSP) [38]	x	x	x	x	x		
Ferdinand et al., 2005 [39]				x			
Fergusson et al., 2005 (CDHS) [40]		x					
Wiles et al., 2006 (NPMS) [41]	x	x	x				
Zammit et al., 2011 (Swedish conscript study) [42]	x						
Rossler et al., 2012 [43]		x					
Gage et al., 2014 (ALSPAC) [44]		x					
Cross-sectional studies							
Rolfe et al., 1993 [45]						x	
Grech et al., 1998 [46]						x	
Degenhardt et al., 2001 [47]	x					x	
Agosti et al., 2002 [48]						x	
Farrel et al., 2002 [49]						x	
Miettunen et al., 2008 [50]	x						
McGrath et al., 2010 [51]	x						
Di Forti et al., 2014 (GAP data 2012) [52]	x						

cohorts [20 23 37 40]. The review found, after adjusting for a comprehensive list of confounding factors, a 40% increase in risk of any psychotic outcome in cannabis users (pooled OR: 1.41, 95%CI 1.20 to 1.65) and a stronger association with heavier or more regular cannabis use (OR: 2.1, 95%CI 1.5 to 2.8). The authors also reported that associations were unlikely to reflect reverse causality because all primary studies excluded people with psychosis at baseline. After the publication of this systematic review some new data have become available, all supporting the causal association between cannabis use and psychosis. Gage et al. [30] have recently updated the estimate provided by Moore et al. [28], by including adjusted results from the Zurich Study [43] and the Avon Longitudinal Study of Parents and Children [44] and found a very similar pooled odds ratio for any psychotic outcome of 1.46 (95%CI 1.24 to 1.72). More recently, Marconi et al. [31] published a new meta-analysis which examined ten studies, six prospective studies [16 19 20 38 41 42], three cross-sectional studies [47 50 51], and one case-control study [52] conducted in seven developed countries across three continents. The authors [31] found that cannabis use is associated with a dose-dependent increase in the risk of psychosis: the risk is doubled in the average user (OR: 1.97, 95%CI 1.68 to 2.31) and quadrupled in the heaviest users (pooled OR: 3.90, 95%CI 2.84 to 5.34). The study controlled for a number of confounders, including age, gender, ethnicity, nicotine smoking, lifetime exposure to drugs other than cannabis, education and employment status.

The reviews without a meta-analysis (see Table I) reported an inconsistent association between cannabis use and psychosis. Macleod et al. [32] reviewed sixteen longitudinal studies, only four of which specifically focusing on the association between cannabis use and psychosis [14 19 20 37] and concluded that the causal nature of this association is far from clear because of flaws in the primary studies: a dose-response relationship was difficult to assess because only binary exposure categories were examined in many of the studies, and the reverse causation hypothesis cannot be excluded because unreported or sub-clinical problems might have preceded cannabis use, even in studies that adjusted for psychological symptoms at baseline. According to the authors [32], it is possible that cannabis use and psychosis might share common antecedents, and that the relationship between cannabis use and psychosis could simply reflect this association. Ben Amar and Potvin [29] reviewed ten longitudinal studies and found that three of them supported a causal relationship between cannabis use and psychosis [14 18 19]; five suggested that chronic cannabis intake increases the frequency of psychotic symptoms, but not of diagnosed psychosis [20 23 38 39 40]; and two showed no causal relationship [22 34]. The authors concluded that although there is evidence that cannabis use increases the risk of developing psychotic symptoms, the causal nature of this association remains unclear; if cannabis use is assumed to be a component cause of a complex series of conditions leading to psychosis or psychotic symptoms, then some factors contributing to this phenomenon might include heavy consumption of cannabis, length of exposure to this drug, early age of first use and psychotic vulnerability. McLaren et al. [33] reviewed the methodological strengths and limitations of ten studies from seven general population cohorts [14 16 18 19 23 37 38 41] which explored the link between cannabis and psychosis and considered research findings against criteria for causal inference. The authors [33] indentified a number of limitations in the studies reviewed, specifically definition of psychosis, consideration of the short-term effects of cannabis intoxication, control of potential confounders and measurement of drug use during the follow-up period. This study [33] confirms that whilst the criteria for causal association between cannabis and psychosis are supported by the studies reviewed, the contentious issue of whether cannabis use can cause serious psychotic disorders that would not otherwise have occurred could not be answered from the existing data. The authors seem rather to suggest that pre-existing vulnerability to psychosis is as an important factor that influence the link between cannabis use and psychosis.

Narrative reviews on the effect of cannabis on the onset of psychosis

Narrative reviews exploring the role of cannabis on the development of psychosis are summarized in Table III.

Based on the available evidence (i.e., the primary studies listed in Table II), most of the narrative reviews published on this topic came to the conclusion that early and heavy cannabis use increases the risk of psychosis in people with genetic/biological vulnerability [1 13 53-64] and that the association is independent from potential confounding factors [54-57 61]. The risk of developing a long lasting psychotic condition is particularly high if the exposure to cannabis starts early in adolescence [65-69]. However, these reviews also indicate that cannabis by itself it is neither a sufficient nor a necessary cause of psychosis. Most of these reviews also indicate that the

Table III. Narrative reviews exploring the role of cannabis on the development of psychosis.

Author(s)	Year	Aim (s)	Type of paper	Study population
Johns [53]	2001	To review the adverse effects of cannabis in the general population and among vulnerable individuals	Narrative review	Adults
Hall and Degenhardt [74]	2000	To evaluate evidence for two hypotheses: (1) cannabis use causes psychosis; (2) cannabis use may precipitate psychosis or exacerbate symptoms	Narrative review	Adults
Degenhardt and Hall [75]	2002	To discuss reasons for the association between cannabis and psychosis by considering the main hypotheses proposed to explain this association	Narrative review	Adults
Smit et al. [54]	2004	To review the role of cannabis use in the onset of symptoms and disorders in the schizophrenia spectrum	Selective review	Adults
Rey et al. [55]	2004	To critically review cannabis research over the last 10 years in relation to rates of use and mental disorders in young people	Narrative review	Adolescents
Hall et al. [76]	2004	To evaluates the existing hypotheses about the relationship between cannabis use and psychosis in the light of recent evidence from prospective studies	Narrative review	Adults
Verdoux and Tournier [56]	2004	To clarify the nature of the link between cannabis use and psychosis	Narrative review	Adults
Verdoux et al. [57]	2005	To examine the impact of substance use on the onset and course of early psychosis	Narrative review	Adults and adolescents
de Irala et al. [71]	2005	To critically analyze the public health relevance of available evidence about the causal relationship between cannabis use and psychosis	Narrative review	Adults and adolescents
Degenhardt and Hall [77]	2006	To assess whether cannabis use in adolescence and young adulthood is a contributory cause of psychosis in that it may precipitate psychosis in vulnerable individuals	Narrative review	Adults and adolescents
Murray et al. [1]	2007	To outline recent research into the endocannabinoid system and to consider the evidence as to whether cannabis can induce acute and chronic psychosis	Narrative review	Adults
Cohen et al. [58]	2008	To review the links between cannabis use and psychosis, drawing upon recent epidemiological, clinical, cognitive, brain imaging and neurobiological research	Narrative review	Adults
Rubino and Parolaro [65]	2008	To examine the existing literature on the long-term consequences of cannabis exposure during adolescence	Narrative review	Adolescents
Henquet et al. [70]	2008	To consider the interplay between genes and exposure to cannabis in development of schizophrenia	Narrative review	Adults
De Lisi [72]	2008	To explore what is known about cannabis's association with schizophrenia, cannabis's effects on the brain, and whether the brain changes present in schizophrenia could be caused by cannabis	Narrative review	Adults
Tucker [59]	2009	To review current knowledge about the relationship between substance misuse and early psychosis	Narrative review	Adults

No. of studies	Time frame	Main findings
n.s.	n.s.	Heavy cannabis use leads to risk of psychotic episode and aggravates the symptoms and course of schizophrenia
n.s.	n.s.	Evidence supports the hypothesis that cannabis use precipitates schizophrenia in persons who are vulnerable because of a personal or family history of schizophrenia or exacerbates the symptoms of schizophrenia
n.s.	n.s.	Evidence suggests that cannabis use may precipitate psychosis among vulnerable individuals, increase the risk of relapse among those who have already developed the disorder, and may be more likely to lead to dependence in persons with schizophrenia
5 longitudinal population-based studies	n.s.	Evidence suggests that cannabis is an etiological cause of psychosis. Cannabis use roughly doubles the risk of becoming schizophrenic; the risk increases when more cannabis is used and in vulnerable people
	1994-2004	Growing evidence suggests that early and regular cannabis use is associated with later increases in depression, suicidal behavior, and psychotic illness and may bring forward the onset of schizophrenia
n.s.	n.s.	It is unlikely that cannabis use can produce psychoses ; cannabis use, however, can precipitate schizophrenia in vulnerable individuals because of a personal or family history
	n.s.	Cannabis exposure is associated with an increased risk of psychosis, possibly by interacting with a pre-existing vulnerability; a dose-response relationship was found and this association was independent from potential confounding factors
n.s.	n.s.	Longitudinal studies found a dose-response relationship between cannabis exposure and risk of psychosis; this association is independent from potential confounding factors
n.s.	n.s.	There are conflicting views about causal relationship. However, the most sensible public health action should be to give counseling against cannabis use to all adolescents, similarly to what is currently being done to prevent the use of tobacco or alcohol
n.s.	n.s.	Regular cannabis use predicts an increased risk of schizophrenia and this relation persists after controlling for confounding variables. It is likely that cannabis use precipitates schizophrenia in individuals who are vulnerable because of a personal or family history of schizophrenia
n.s.	n.s.	Epidemiological evidence strongly suggests that heavy cannabis use increases the risk of both psychotic symptoms and schizophrenia. Cannabis acts as a component cause that increases the risk of psychotic illness between 1.4 and 1.9 times, and that might account for between 8 and 14% of cases of schizophrenia in different countries
n.s.	n.s.	Cannabis use increases the risk of psychosis by 40%; approximately 14% of psychotic outcomes in young people would not have occurred if cannabis had not been consumed
n.s.	n.s.	Pubertal cannabis use in vulnerable individuals may act as a risk factor for inducing enhanced behavioral disturbances related to schizophrenia
n.s.	n.s.	Mechanisms of gene-environment interaction are likely to underlie the association between cannabis and psychosis. Multiple variations within multiple genes, together with other environmental factors (eg, stress), may interact with cannabis to increase the risk of psychosis
n.s.	n.s.	The evidence from epidemiological studies is inconsistent and not conclusive that cannabis causes schizophrenia and thus the issue is still highly controversial. Further research is needed to determine the biological effect that cannabis has on the brain in people who do or do not develop schizophrenia
n.s.	n.s.	Cannabis appears to confer increased likelihood of developing schizophrenia in biologically vulnerable individuals

follows

continue Table III

Author(s)	Year	Aim (s)	Type of paper	Study population
Sewell et al. [60]	2009	To review the evidence supporting and refuting the association between cannabis exposure and psychotic disorders	Narrative review	Adults
D'Souza et al. [61]	2009	To review clinical and preclinical studies investigating cannabis use as a risk factor for the development of psychosis	Narrative review	Adults
Shapiro and Buckley-Hunter [66]	2010	To explore the relationship between cannabis and the onset of psychosis	Narrative review	Adults and adolescents
Gururajan et al. [62]	2012	To review clinical and preclinical studies investigating cannabis or methamphetamine use as a risk factor for the development of psychosis	Narrative review	Adults
Rubino et al. [67]	2012	To review clinical and preclinical studies investigating cannabis use as a risk factor for the development of psychiatric disorders in adolescents	Narrative review	Adolescents
Parakh and Basu [63]	2013	To review studies exploring the association between cannabis use and psychosis	Narrative review	Adults
Burns [64]	2013	To examine causality, the neurobiological basis for such causality and for differential inter-individual risk, the clinical and cognitive features of psychosis in cannabis users	Narrative review	Adults
Gage et al. [73]	2013	To consider the evidence for a causal relationship between cannabis use and psychosis and to discuss the issue in a public health perspective	Narrative review	Adults and adolescents
Radhakrishnan et al. [68]	2014	To review existing literature on the association between cannabis and psychosis	Narrative review	Adolescents
Wilkinson et al. [69]	2014	To review the evidence investigating the association between cannabis and psychotic disorders with special attention to literature from the past three years	Narrative review	Adults and adolescents
Volkow et al. [13]	2014	To review the current state of the science related to the adverse health effects of the recreational use of cannabis, focusing on those areas for which the evidence is strongest	Narrative review	Adults and adolescents
Ksir and Hart [78]	2016	To review research on cannabis and psychosis, with specific emphasis to how studies provide evidence relating to the hypothesis of (1) cannabis as a contributing cause, and (2) shared vulnerability	Narrative review	Adults and adolescents
Volkow et al. [13]	2016	To identify what is known and not known about the effects of cannabis use on human behavior, including cognition, motivation, and psychosis	Narrative review	Adults and adolescents

ECA: Epidemiological Catchment Area study (USA); NEMESIS: Netherlands Mental Health Survey and Incidence Study (NL); CHDS: Christchurch Health and Development Study (New Zealand); EDSP: Early Developmental Stages of Psychopathology (Germany); NPMS: National Psychiatric Morbidity Survey (UK); GAP: Genetics and Psychosis study (UK); ALSPAC: Avon Longitudinal Study of Parents and Children (UK).

No. of studies	Time frame	Main findings
n.s.	n.s.	Cannabis use is a component cause that may induce psychotic disorders. However, cannabis is neither necessary nor sufficient to do so alone. Further work is needed to identify the factors that underlie individual vulnerability to cannabis and to elucidate the biological mechanisms underlying this risk
n.s.	n.s.	Early and heavy cannabis use may increase the risk of developing psychosis. However, the mechanisms by which exposure to cannabis increase the risk for psychosis are unknown and warrants further research
n.s.	n.s.	Cannabis is a significant risk factor in the etiology of psychosis; adolescents are more vulnerable to using cannabis
n.s.	n.s.	Literature support the existence of causation between cannabis and schizophrenia. However, further studies are needed to provide a greater insight into the mechanisms that mediate the long-term and neurodevelopmental effects of cannabis
n.s.	n.s.	Early cannabis use in adolescence is closely related to increased risk of later psychiatric problems (cognitive abnormalities, psychosis, mood disorders), especially in vulnerable people. Further studies are needed to clarify the mechanisms underlying the effect of cannabis on the adolescent brain
n.s.	n.s.	Cannabis use increases the risk of psychosis in people with genetic or environmental vulnerability. However, cannabis by itself it is neither a sufficient nor a necessary cause of psychosis
n.s.	n.s.	Early-initiated, lifelong cannabis use in vulnerable individuals may lead to a psychosis virtually indistinguishable from schizophrenia at onset. In those whose cannabis use persists, a chronic deteriorating disorder seems to follow (in these cases one may conclude that cannabis has been played a causal role). Recent use of cannabis in vulnerable individuals, just prior to psychosis onset, is clinically distinguishable from schizophrenia at first-episode; ceasing cannabis use after the first-episode have an excellent prognosis with full recovery
n.s.	n.s.	Consistent evidence shows that individuals who use cannabis have an increased risk of psychotics. However, the role of cannabis in the aetiology of schizophrenia remains uncertain given the limits of observational epidemiology
n.s.	n.s.	Exposure to cannabis in adolescence confers a higher risk for psychosis in later life and the risk is dose-related
n.s.	2011-2013	Exposure to cannabis in adolescence is associated with a risk for later psychotic disorder in adulthood; this association is consistent, temporally related, shows a dose-response. However, cannabis is neither necessary nor sufficient to cause a persistent psychotic disorder; it is probably a component cause that interacts with other factors
n.s.	n.s.	Cannabis use is associated with onset of psychosis, especially among people with a preexisting genetic vulnerability, and exacerbates the course of illness in patients with schizophrenia. However, it is difficult to confidently attribute the increased risk of psychosis to cannabis use
n.s.	n.s.	Cannabis does not in itself increase the risk for psychosis; evidence seems to suggest that both early use of cannabis and heavy use of cannabis are more likely in individuals with a vulnerability to a variety of other problem behaviors; the same vulnerability also results in increased risk for psychosis or some other mental disorder in some individuals
n.s.	n.s.	Prospective, longitudinal, epidemiological studies consistently report an association between cannabis use and schizophrenia. While cannabis use is neither necessary nor sufficient for the development of schizophrenia, available evidence suggests that cannabis use may initiate the emergence of a lasting psychotic illness in individuals with a genetic vulnerability

mechanisms by which exposure to cannabis increase the risk for psychosis are stills unknown and warrants further research [60-63]. Mechanisms of gene-environment interaction are likely to underlie the association between cannabis and psychosis. Multiple variations within multiple genes, together with other environmental factors (eg, stress), may interact with cannabis to increase the risk of psychosis [70].

Other reviews are more cautious in attributing the increased risk of psychosis to cannabis use [13]. According to some authors the evidence from epidemiological studies is still inconsistent and not conclusive [71-73]. It seems unlikely that cannabis use can produce psychoses, it is more likely that cannabis use precipitates psychosis in individuals who are vulnerable because of a personal or family history [74-77]. Ksir and Hart [78] maintain that cannabis does not in itself increase the risk for psychosis; they rather suggest that both early use of cannabis and heavy use of cannabis are more likely in individuals with a vulnerability to a variety of other problem behaviors (the same vulnerability also results in increased risk for psychosis or some other mental disorder in some individuals). All these authors, however, consistently suggest that further research is needed to better understand the associations between cannabis and psychosis and the possible mechanisms underlying this association.

Effect of cannabis on transition to psychosis in clinical high risk populations

People at clinical high risk for psychosis represent an ideal population in which to investigate the putative role of cannabis use in the onset of psychosis, as 20-35% will develop the disorder within a few years following clinical presentation [79]. So far three systematic reviews on studies exploring the effect of cannabis use on transition to psychosis in clinical high risk individuals have been published. Their main results are summarized in Table IV.

The first review [80], included eleven studies, reported mixed results: some research found that cannabis use was associated with more severe symptoms at baseline, increased pre-psychotic symptoms immediately after intoxication, and earlier onset of certain high-risk symptoms, whereas other studies did not report any significant association between cannabis use and baseline symptoms. Four out of five studies reported no significant effect of cannabis use on transition to psychosis. The second review [81] reported that the majority primary studies did not found a role for cannabis use in later conversion to psychosis: among the ten studies reviewed only two reported a significant association between lifetime cannabis use and transition to psychosis [82 83]. More recently, Kraan et al. [84], in a systematic review and meta-analysis of seven prospective studies with a follow-up duration of 1-4 years, reported that lifetime cannabis use was not significantly associated with transition to psychosis (OR: 1.14, 95%CI 0.86 to 1.52); however, current cannabis abuse or dependence were associated with increased risk of transition into psychosis in subjects at ultra high risk of psychosis (OR: 1.75, 95%CI 1.135 to 2.71). The major limitation of literature examining the impact of cannabis use on transition to psychosis is the lack of control for potentially confounding factors. Some of the potential control factors would include method of ascertainment of subjects, inclusion and exclusion criteria particularly, age of participants which typically vary from 12 to 31, age at first use of substances particularly cannabis, assessment of substance use which should include type and quantities and possibly biological measures, co-morbid diagnoses (e.g. mood disorders), medications including antipsychotics and other potential risk factors such as family history. Inconsistencies found in this literature

Table IV. Systematic reviews exploring the role of cannabis on the transition to psychosis in at-risk populations.

Author(s)	Year	Aim(s)	Type of paper	Study population
van der Meer et al. [80]	2012	To review studies measuring the impact of cannabis use on CHR symptoms and transition to a first psychotic episode	Systematic review	Adolescent (Clinical High Risk)
Addington et al. [81]	2014	To review studies measuring patterns and rates of substance use in CHR individuals and the effects on the transition to psychosis	Systematic review	Adolescent (Clinical High Risk)
Kraan et al. [84]	2016	To understand the role of cannabis use on transition to psychosis in UHR individuals	Systematic review and meta-analysis	Adolescent (Ultra High Risk)

highlight the need for further work in clinical high risk samples in order to understand the role of cannabis use in the onset of psychosis. Future work investigating cannabis use in the clinical high risk group should seek to determine, through repeated assessment of substance use alongside other potential risk factors and multiple outcomes, the interplay between cannabis, pre-existing vulnerability for psychosis, and symptom expression in the onset of psychosis.

Discussion

Main findings

Most of the systematic reviews considered in this paper consistently report a significant association between cannabis use and psychosis which could be indicative of a causal relationship [25-29 31], or at least suggest that the possibility of such a relationship cannot be excluded [30 32]. Overall, people using cannabis have at least a two-fold risk of developing psychosis compared to people who do not use it [25-31] and the risk is increased (at least four-fold) among the heaviest users [28-31].

However, the primary cohort studies considered in these reviews have a number of methodological limitations and therefore caution should be used when interpreting results. The first published systematic review of cannabis use and psychosis included cross-sectional studies and did not address study quality [27]. Another systematic review examined broader psychosocial outcomes, but the lack of focus specifically on psychotic disorders meant that the explanations for associations could not be examined in detail [32]. Early meta-analyses from both systematic [27] and narrative [25 26] reviews included cross-sectional data [25 26] or used unadjusted results [27] and combined effects for ever-use of cannabis with those for dependence [25-27]. As might be expected, all report larger effects than observed in Moore et al. [28] and, more recently, in Marconi et al. [31], although direct comparison of these effects is difficult.

There is also indirect evidence that supports causality. For example, a number of primary studies [18-20] included in the reviews considered here found evidence for specificity of exposure, namely that associations between other drug use and psychosis are weaker than for cannabis. There is also some evidence of specificity of outcome [28], though this is not seen in all studies [30]. Research has also shown that associations between cannabis use and psychotic symptoms are not reducible to family history of psychosis [14 15 18 28 31] and – most important – that genetic liability for psychotic disorder does not predict cannabis use [85]. However, even if the association between cannabis and psychosis is causal, cannabis is neither necessary nor sufficient to cause psychotic disorder; risk factors for multifactorial complex disorders, such as psychosis, are not deterministic and in this context cannabis may be seen as "a component cause" for the development of psychotic disorder or psychotic symptoms [86].

The role of genetic predisposition

As cannabis use is neither necessary nor sufficient for the development of psychosis, it has been suggested that cannabis may induce the onset of enduring psychotic disorders in individuals with a genetic vulnerability. Mechanisms of gene-environment interaction are likely to underlie the association between cannabis and psychosis: Caspi et al. [37] found that cannabis use during adolescence was associated with an increased risk of developing psychosis during adulthood among individuals carrying the COMT Val/Val genotype, to a lesser extent among Val/Met individuals, but not among Met/Met individuals. These cannabis x COMT

No. of studies	Time frame	Main findings
11 studies	Up to 2011	Cannabis use seems to provoke and enhance subclinical symptoms in CHR subjects. However, the results provide no consistent evidence for an association between cannabis use and transition to a first psychosis in CHR subjects
10 studies	Up to 2013	Limited evidence was found to suggest that increased rates of substance use may be associated with transition to psychosis. However, further prospective research examining the association between substance use and transition to psychosis is required before any firm conclusions can be made
7 cohort studies	Up to 2015	Cannabis use is predictive of transition to psychosis only in those meeting criteria for cannabis abuse or dependence (OR 1.75, 95% CI 1.13 to 2.71), thus suggesting a dose-response relationship between current cannabis use and transition to psychosis

Val158Met interactions were replicated in several [78 87-90], but not in all studies [42 91 92]. The results supporting the hypothesis that some gene variants influence the likelihood of developing schizophrenia contingent on certain environmental exposure (eg, cannabis use) reflect tentative findings among small numbers of individuals that require replication [93]. Alternatively, Ksir and Hart [78] suggest that both psychosis and cannabis use are more likely in individuals with a shared vulnerability to misuse of various substances and increased risk for various mental disorders. In other words, the correlation between cannabis use and psychosis is not specific, either with regard to the chemicals found in cannabis or to psychosis as opposed to other disorders. However, two recent GWAS studies [94 95] suggest that the overlap in genetic vulnerability for psychosis and cannabis use is likely to be only modest. Thus, should there be any shared genetic vulnerability between cannabis use and schizophrenia, it could explain only a small proportion of the association between the two [96].

Some criticisms to causal explanation

One argument against cannabis having a causal role in psychosis is that cannabis use became more common in the latter part of the 20th century without an obvious change in the incidence of schizophrenia [21]. There is little reliable evidence on temporal trends in the incidence of schizophrenia and related psychoses, so it is difficult to establish whether this statement is true or not. Some studies reported that incidence of schizophrenia and related psychosis has increased in recent decades [97], while others have found no change or a decrease [98-100]. Ecological studies provides only very weak evidence for causality, as it cannot be ascertained whether individuals using cannabis are the same as those experiencing psychosis (the ecological fallacy); moreover these studies are unable to account for likely confounders, and do not account for other potentially competing risk factors for schizophrenia that may have declined over the same time period [30]. Whether preventing cannabis use will have any substantial impact on preventing psychotic disorders in the population, or within specific subgroups at risk, is yet to be adequately determined [73]. What we do know is that the incidence of schizophrenia and other related psychosis is significantly higher in countries such, as England [101] and The Netherlands [102], where high potency cannabis has taken over the market [103] compared with other countries, such as Italy [104 105], where more traditional forms of cannabis are smoked [106].

High potency cannabinoids

The use of high potency cannabis is currently widespread across some European countries and represents a critical issue. The cannabis plant produces at least 80 chemicals, and the two best known (THC and cannabidiol [CBD], a cannabinoid that seems to offset some of the adverse effects of THC) vary not only in their strength but also in their ratio in different types of cannabis. Over the last 5 decades, selective breeding has increased the concentration of THC in the cannabis available in many countries. For example, the THC content of cannabis in the 1960s in England and The Netherlands was around 3%; high potency varieties now available average 16% in England [107] and 20% in The Netherlands [108]. Furthermore, traditional hash (resin) contains THC and a similar proportion of CBD, but new varieties ('skunk') have high levels of THC, but practically no CBD [86]. Recent research conducted in England found that people using high-potency cannabis on a daily basis are five times more likely than non-users to suffer from a psychotic disorder [109]. This finding has increased concern that as levels of THC in cannabis have altered over the past few decades, results from earlier studies could be underestimating the impact of the effects of cannabis on psychosis that exist today.

A public health perspective

If the overall rate of schizophrenia in the population is about 1% and if the association between cannabis and schizophrenia is causal and of the magnitude estimated across studies to date [28 31], this would equate to a schizophrenia lifetime risk of approximately 2-3% in regular cannabis users (though risk for broader psychotic outcomes will be greater). The risk could be much greater in those at a higher genetic risk [110] or in those who use high-potency cannabis [109]: if regular cannabis use increased the risk of schizophrenia twofold and assuming the pattern of risk for co-exposure to cannabis and high genetic risk is approximately multiplicative, as it is for most risk factors for multifactorial complex disorders, then the lifetime risk in individuals with a first-degree relative if they use cannabis regularly could be around 20%. This is a cause of concern for mental health care provision. Given the potential of millions of new cannabis users, the above mentioned estimates translate into several thousands of individuals with quite disabling psychotic symptoms at a time when mental health services, in most European countries are facing a major crisis due to a dramatic reduction in funding and resources.

There remains argument over the proportion of psychosis that could be prevented if nobody used cannabis. The population attributable fraction (PAF) measures the population effect of an exposure by providing an estimate of the proportion of disorder that would be prevented, assuming casualty, if the exposure was removed. The PAF depends on both the prevalence of exposure (ie, measures of cannabis use) in cases and the odds ratio (OR) for the exposure, such that a risk factor with a modest OR can have a major population effect if the exposure is common. Estimates of the PAF suggest that from 8 to 24% of psychosis in different countries could be prevented if cannabis use was prevented, depending on whether risk is confined to heavy cannabis or all users. The PAF for the Dunedin study in New Zealand [25] was 8%. Henquet et al. [26] calculated that the PAF for individuals in the general population in Germany with a predisposition for psychosis was more than double (14%) that of the total population (6%). Moore et al. [28], based on the proportion of adolescents and young adults in the UK who have ever used cannabis (40%) and on the risk of a psychotic outcome for having ever used cannabis, estimated that about 14% of psychotic outcomes in young adults would not occur if cannabis were not consumed. More recently, Di Forti et al. [109] reported an increased estimate for the PAF accounted for by cannabis (24%) compared with previous studies; this finding could be caused by, not only the greater use of cannabis, but also the greater use of high-potency ('skunk') cannabis in south London. All such estimates, however, rely on the assumption that the association between cannabis use and psychosis is causal, and that the relative risk is an accurate estimate of this causal effect.

Policy implications

A causal relationship between cannabis use and psychotic disorders may not be still proven 'beyond reasonable doubt', but in the absence of any specification of plausible uncontrolled confounders there are good reasons for believing that cannabis is much more likely than not to be a contributory cause of these disorders. The epidemiological evidence and the biological plausibility of the relationship are strong enough to warrant giving advice to young people about this possible risk, along with information on other potential adverse effects of cannabis. The potential effects of a psychotic illness on a young person's life chances are so substantial that it would be socially irresponsible not to do so [111].

How strong must the evidence for a causal relation between cannabis and psychosis be before taking action would be justified? If the standard of proof we require for action is 'beyond reasonable doubt', then we would find it difficult to make any policy decisions according to the available evidence. If, however, we are prepared to act on the balance of probabilities (more likely than not), some policy action is warranted [112]. Prevention is better than treatment. In this regard, it is worth recalling the many years it took for cigarette smoking to be accepted as a cause of lung cancer and that 4 decades passed before serious attempts were made to persuade people to stop smoking tobacco [86]. By the same sort of prudential reasoning, it would be arguably good social policy to encourage young people to avoid using cannabis or, at the least, to delay their use into early adulthood [71]. Young adolescents seem more vulnerable to the effects of cannabis. The Dunedin cohort study [20] found a stronger association between cannabis use and the development of psychotic symptoms among individuals who first used cannabis before the age of 16. These observations could be related to the fact that cannabis is particularly harmful to the brain during its critical period of development earlier in adolescence [65 67 68]. An early age of exposure to cannabis is a contributing factor to the precocious onset of a first psychotic episode, as confirmed by the meta-analysis of Large et al. [113] which found an earlier age at onset of psychosis (nearly three years) in people using cannabis compared to non users. The same research group also found that the effect of cannabis is specific, since other substances such as alcohol or tobacco are not associated with a younger age at onset of psychosis [114]. Thus reducing the use of cannabis could be one of the few ways of altering the outcome of psychosis because earlier onset is associated with a worse prognosis and because other factors associated with age at onset, such as family history and sex, cannot be changed [115]: an extra two or three years of psychosis-free functioning could allow many patients to achieve the important developmental milestones of late adolescence and early adulthood that could lower the long-term disability arising from psychotic disorders [113]. For the above mentioned reasons it makes a good case to discourage cannabis use amongst young people, whilst there is room for disagreement about what the best means of achieving this goal are [32 112].

Conclusions

Recent changes to cannabis legislation in some states of the USA will provide a number of natu-

ral experiments of both the risks and benefits of decriminalizing marijuana and legalizing the supply of cannabis [86]. The next decade will provide an opportunity to document both the benefits and risks associated with the changing legal landscape regarding cannabis use. Given the emerging evidence concerning the adverse effects of cannabis use, and the fact that the legalization of the drug could arguably increase the level of risk posed by cannabis use, it is critical that these changes in cannabis legislation are monitored and evaluated through well-designed studies that are able to assess the impact of these law changes both at individual and population levels [116].

Further steps to legalize cannabis use will inevitably lead to increased availability, thereby facilitating increased use, perhaps among individuals that might not have tried cannabis otherwise. Although current scientific evidence may not be sufficient to support a complete public policy reversal on cannabis, it should cause concern among policy makers, health care professionals, and educators.

Take home messages for psychiatric care

- Cannabis use is causally associated with at least a two-fold risk of developing psychosis
- The risk is further increased in people with genetic/biological vulnerability, who start using cannabis early in adolescence and who heavily use cannabis (or use high potency cannabis)
- Cannabis by itself it is neither a sufficient nor a necessary cause of psychosis (it is rather a component cause)
- Cannabis use should be discouraged among young people and subjects vulnerable to psychosis

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