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ORIGINAL PAPER

Cannabis use and psychosis: a review of reviews

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Abstract

We conducted a systematic review of meta-analyses and systematic reviews to evaluate the impact of cannabis use on the onset and course of psychoses. Following a systematic literature search of five data bases (2005–2016) and consecutive structured evaluation, we were able to include 26 systematic reviews and meta-analyses. The methodological quality of the included publications were in the range of high and poor. The scientific literature indicates that psychotic illness arises more frequently in cannabis users compared to non-users, cannabis use is associated with a dose-dependent risk of developing psychotic illness, and cannabis users have an earlier onset of psychotic illness compared to non-users. Cannabis use was also associated with increased relapse rates, more hospitalizations and pronounced positive symptoms in psychotic patients. We make recommendations about the type of research that is required to better characterize the relationship between cannabis use and the development and outcomes of psychosis.

Keywords Psychosis · Schizophrenia · Cannabis · Cannabinoids · THC · CBD · Evidence-based medicine

Introduction

Psychotic experiences include among other symptoms, hallucinations of all modalities, delusions, disorganization, thought disorder and psychotic fear. These symptoms are observed in several psychiatric disorders, but especially in schizophrenia and other related psychoses. Clinical and subclinical psychotic symptoms that are self-limiting, but also may persist, following the use of cannabis are clinically well-known phenomena that were described in observational and interventional studies (e.g., [1–3]). From more than 100 described phytocannabinoids, Δ(9)-tetrahydrocannabinol [Δ(9)-THC] is the main psychoactive molecule inducing the described psychotic symptoms [4]. In this context, the question whether the recreational use of cannabis, cannabis abuse or dependency can cause transient or persistent psychotic disorders is one of most discussed and debated questions in the field [5–8]. This question has not only implications for research and clinical care but is of utmost importance for cannabis users, healthcare systems and society.

It has been suggested that cannabis is associated with increased odds of psychotic disorder [9], that it has an unfavorable impact on the disease outcomes and that it is related to reduced social functioning [10]. However, the strength of the observed associations still remains elusive given the

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heterogeneity of definitions (e.g., psychosis vs. schizophrenia; psychotic experiences in healthy users vs. worsening of psychosis in schizophrenia patients), the variability in observations periods and different measures of the frequency of cannabis intake (continuous use vs. intermittent use) make it difficult to provide precise statements [11]. The situation becomes even more complex bearing in mind that persistent psychosis may not be schizophrenia in every case and that while cannabis-induced psychotic episodes can be transient they are also a risk factor for developing schizophrenia [12]. Cannabis use also has a high prevalence in patients with diagnosed schizophrenia [13, 14]. It is indisputable that there is no single cause of the onset of a transient or persistent psychotic episode or psychotic illness [15]. It is the interaction of multiple environmental, developmental and genetic factors that define the individual vulnerability to developing schizophrenia [16, 17].

Publications on cannabis and psychoses continuously increased in the past decade. Most health care providers, patients or stakeholders do not have the time to read this large number of studies to make clinical or public health decisions. They increasingly turn to systematic reviews and meta-analyses for a summary the current scientific knowledge. In recent years, however, decision makers who were once overwhelmed by the number of individual studies have become faced by a flood of reviews [18]. More recently, calls have been made for 'rapid reviews' to provide decision-makers with the evidence they need in a shorter time frame [19]. To bring together reviews on "cannabis use and psychoses" and to shed more light into the complex relationship between cannabis use/abuse and the development of psychotic symptoms and syndromes, we conducted a systematic review of reviews. Five clinical topics were addressed. First, does the prevalence of psychotic disorders differ between cannabis users and non-users in the population? Second, do cannabis users have earlier onsets of psychotic illnesses than non-users? Third, what is the proportion of cannabis use in patients with psychotic illnesses? Fourth, what are the differences between patients with psychotic illnesses who do and do not use cannabis users in the symptomatology and outcomes of their illnesses? Fifth, is there evidence for a biological link between the use of cannabis and the development of a psychotic illness?

Methods

This narrative review is part of an expertise [Cannabis: Potential and Risks: A scientific analysis (CaPRis)] commissioned by the German Ministry of Health [20]. It followed guidance published by the Cochrane Collaboration [21, 22]. Other parts of this expertise were published beforehand in a special issue of this journal [23]. Screening of the search results, assessing eligibility and methodological quality of full-text articles, data extraction and data synthesis were independently performed by two reviewers; disagreements were resolved through consensus or referral to a third reviewer.

Rationale

According to the German Association of the Scientific Medical Societies (AWMF) [24] the rationale of this work followed a top-down search strategy. We prioritized to identify studies with the highest level of evidence, i.e., aggregated data in systematic reviews and meta-analyses [25]. If no such studies are found to answer the clinical questions, the search strategy included studies with a lower level of evidence (e.g., cohort studies, case control studies).

Eligibility criteria

The inclusion criteria were systematic reviews or meta-analyses focusing on the use of cannabis and psychoses, published since 2006, research conducted on humans, available data on the effects and side-effects of cannabis, in the English or German languages. To summarize the findings of published research on "cannabis and psychoses" and to account for a bidirectional relationship, we included the populations with different cannabis use patterns (lifetime, past year, past month, daily use, intensive use, occasional use) and any kind of psychosis (acute psychosis, psychotic disorders, schizophrenia). We did not specify outcome criteria. We excluded non-systematic reviews, reviews without a documented systematic literature search, systematic reviews not focusing on cannabis/cannabinoids, animal and molecular studies, as well as expert opinion and position statements.

Information sources

A search in PubMed, PsycINFO, Medline, Embase and the Cochrane Library from 2005 until 2016 was performed. References of the identified reviews and meta-analyses were hand-searched to identify additional studies. Researchers in this field were contacted.

Search

For the global search were used a combination of search terms (MeSH-Terms) describing cannabis: "Cannabis OR cannabinoid* OR hemp OR hanf" OR 2) "Mariuana OR Marihuana OR Marijuana". Search strings were built, pilot-tested and adopted to the different databases.

Study selection

The search process was documented in a prior defined research protocols. The titles and the abstracts of each detected citation were screened manually. The full texts of each potentially relevant citation were retrieved for detailed review and eligibility and methodological quality of full-text articles was assessed. A standardized form was used to extract data from the included studies and to synthesize data. Evidence synthesis followed the PICO scheme (i.e., baseline characteristics of participants, indication, comparisons and outcomes). Other research parameters (e.g., types of included studies), population and sample collection, demographic information (age, gender), other key outcome variables and sources of funding were also extracted.

The PRISMA checklist [26] can be found in supplement and all materials are available upon request. The study selection process (i.e., screening, eligibility, inclusion in review) was documented in PRISMA flow-charts. References are archived in EndNote™ (EndNote X8, Clarivate Analytics). For more information on background, rationale, methods and materials see [20]. Prior to study initiation, the study protocol was registered with the Centre for Reviews and Dissemination at the University of York https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=33249). A list of the excluded publications can be found in supplementary material.

Exclusion of duplicate primary studies

Reviews were screened to exclude systematic reviews with duplicate primary studies. If duplicate primary studies were identified, the review was included according to the following preference criteria [27]: the availability of numerical data or results; the highest SIGN-rating (Quality assessment tool for systematic reviews); most recent date of publication; larger number of studies and observations included. These criteria were important where more than one systematic review had been published within a specialty. Assessments were made independently for each outcome, so that if two reviews, with duplicate primary studies, reported on different outcomes, both reviews were eligible for inclusion.

Risk of bias and summary measures

Each publication was reviewed using the Scottish Intercollegiate Guidelines Network (SIGN) methodology checklist [28]. The quality of the source publications included in the detected 26 publications was evaluated with regard to the levels of evidence (LoE) using the Oxford Centre for Evidence-Based Medicine grading [25]. Our review applied a qualitative data synthesis approach. High heterogeneity of primary outcome measures in the identified studies hindered an aggregated data analysis. The study results were interpreted with respect of their sample size, level of evidence, risk of bias and level of heterogeneity/homogeneity.

Results

We were able to include 26 systematic reviews and meta-analyses. Please see Table 1 for a detailed description of the included publications and Fig. 1 for the PRISMA chart. We selected a total of 26 publications. 15 of the total number of selected publications included a meta-analytic approach [10, 29–42]. The remaining 11 publications were all systematic reviews without meta-analysis [43–53]. The highest level of evidence (LoE) of 1 according to OECEBM was assigned to the three out of 26 publications [10, 31, 53]. In general, evidence grades differed substantially across publication mainly because of differences in study types. The largest meta-analyses included 66,816 participants [34], and the largest systematic review 113,802 participants [41].

Do cannabis users and non-users show differences in the occurrence of psychotic illnesses?

The use of cannabis can induce self-limiting psychotic episodes, but from a clinical perspective the important question is whether cannabis use can produce persistent psychotic disorders. To answer this first research question, we analyzed five meta-analyses [31, 33–35, 41] and one systematic review [44].

Kraan et al. [31] (SIGN++, LoE1) included seven prospective longitudinal studies with a total of 1171 at-risk subjects. They were not able to find a statistical relationship between lifetime cannabis use and the risk of developing psychosis (OR = 1.14, 95% CI 0.856–1.524, $p = 0.37$). However, they found that patients who fulfilled the criteria for cannabis abuse or dependency had an increased risk of developing psychosis (OR = 1.75, 95% CI 1.135–2.710, $p = 0.01$) [31]. Linscott and van Os [33] (SIGN+, LoE3) included 61 cohorts and were able to detect elevated prevalence (OR = 2.51, 95% CI 1.84–3.43) and incidence rates (OR 1.77, 95% CI 1.20–2.61) for psychotic experiences in those subjects who also used cannabis.

Marconi et al. [34] (SIGN+, LoE4) included ten studies in their meta-analysis and showed based on a logistic regression model that the risk for schizophrenia and other psychosis-related outcomes was increased among the heaviest cannabis users in comparison to non-users (OR = 3.90, 95% CI 2.85–5.34). Persons with lifetime cannabis-use had an OR of 1.97 (95% CI 1.68–2.31) indicating a relationship between dosage and outcome.

Moore et al. [35] (SIGN+, LoE4) investigated a total of 35 studies. Based on cohort studies they detected an

Table 1 Alphabetical list of the included studies

Nr	References	Type	*N*/*n*	OCEBM LoE	SIGN methodological rating
1	Baldacchino et al. [43]	Systematic review	8/614	3	++
2	Ben Amar and Potvin [44]	Systematic review	20/3283	4	–
3	Burns [29]	Meta-analysis	7/1453	4	–
4	Cookey et al. [45]	Systematic review	18/1258	4	+
5	Ferretjans et al. [46]	Systematic review	19/1432	4	+
6	Geoffroy et al. [47]	Systematic review	2/nr	4	+
7	James et al. [48]	Systematic review	24/932	4	+
8	Koskinen et al. [30]	Meta-analysis	35/5540	4	++
9	Kraan et al. [31]	Meta-analysis	7/1171	1	++
10	Large et al. [32]	Meta-analysis	83/22,519	4	+
11	Linscott and van Os [33]	Systematic review Meta-analysis	95/> 9500 3/> 300	3	+
12	Malchow et al. [49]	Systematic review	16/500	3	+
13	Marconi et al. [34]	Meta-analysis	10/66,816	4	+
14	Moore et al. [35]	Meta-analysis	35/nr	4	+
15	Myles et al. [37]	Meta-analysis	40/18.578	4	+
16	Myles et al. [36]	Meta-analysis	40/6321	4	+
17	Potvin et al. [38, 39]	Meta-analysis	20/3283	4	+
18	Rapp et al. [50]	Systematic review	19/1432	4	++
19	Sara et al. [40]	Meta-analysis	40/6321	4	++
20	Schoeler et al. [10]	Meta-analysis	24/16,565	1	++
21	Semple et al. [41]	Meta-analysis	11/113,802	4	+
22	Sara et al. [40]	Meta-analysis	40/6321	4	++
23	Serafini et al. [51]	Systematic review	45/nr	4	+
24	Szoke et al. [42]	Meta-analysis	29/nr	3	+
25	Uliana et al. [52]	Systematic review	14/7767	4	+
26	Zammit et al. [42]	Systematic review	10/nr	1	++

nr, not reported; *N*, number of included studies; *n*, total sample size; SIGN, ++ high quality, + acceptable, – low quality; OCEBM, Oxford Centre for Evidence-Based Medicine; LoE, Level of Evidence

increased risk of psychotic outcomes in subjects who ever used cannabis (OR = 1.41, 95% CI 1.20–1.65). Subjects who used cannabis most frequently had a high risk for psychotic outcomes (OR = 2.09, 95% CI 1.54–2.84), suggesting a dose-dependent effect.

Semple et al. [41] (SIGN+, LoE4) included 11 prospective studies and performed a meta-analysis based on seven studies which showed an OR of 2.9 (95% CI 2.4–3.6) for a relationship between cannabis use and psychosis. Moreover, an OR of 3.1 (95% CI 1.7–5.5) was estimated for subjects who had used cannabis more than 50 times, indicating again a dose-outcome relationship. The systematic review of Ben Amar and Potvin [44] (SIGN–, LoE4) included 10 studies which had a significant overlap with a previously discussed publication [41] and found an increased risk of developing psychosis after using cannabis, especially in young people.

In summary, the evaluated publications indicate, that cannabis users have a dose-dependent risk of developing a psychosis, but more longitudinal studies with longer observation periods are needed.

Do cannabis users have earlier onsets of psychotic illnesses than non-users?

This question is of the highest clinical importance because earlier onsets of psychosis are associated with poorer longitudinal outcomes. We identified two meta-analyses [32, 37] that addressed this second research question. Large et al. [32] (SIGN+, LoE4) showed in 8167 substance-using patients compared to 14,352 non-substance-using patients that cannabis users had an age at psychosis onset that was 2.70 years earlier than those who had not used cannabis, ($p < 0.001$). A similar relationship was not found for alcohol-users ($p = 0.64$), but it was for unspecified substance users (2.00 earlier onset, $p < 0.001$) [32]. Myles et al. [37] (SIGN+, LoE4) analyzed 40 studies with a high heterogeneity and found that the age of onset of psychosis was

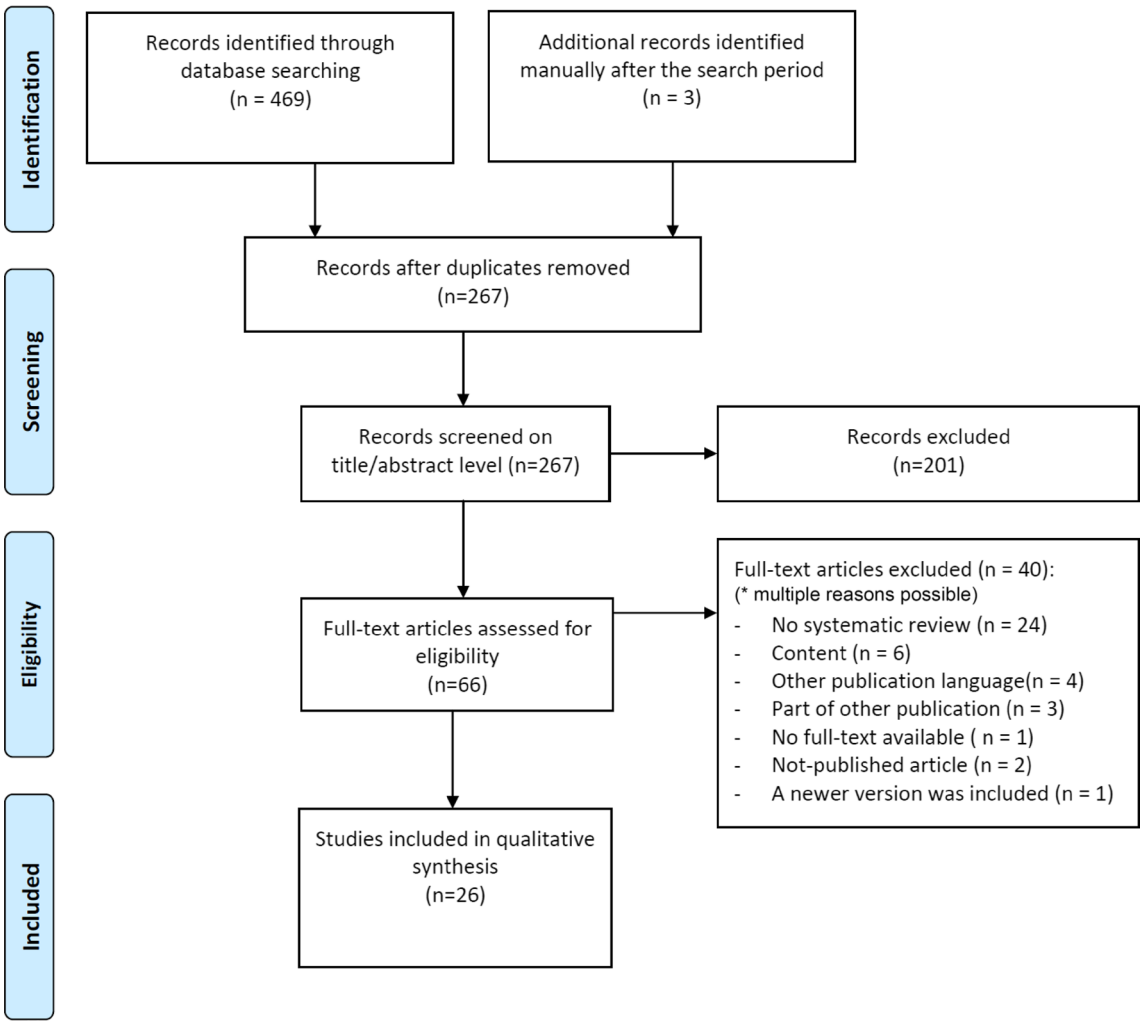

Fig. 1 PRISMA flow diagram

32 months earlier in 3199 cannabis users compared to 5715 non-users (SMD = − 0.399, 95% CI − 0.493 to − 0.306, $p < 0.001$) [37]. This relationship was not found for tobacco users (SMD = 0.002, 95% CI − 0.094 to 0.097, $p = 0.974$). In summary, the two meta-analyses indicate that on average cannabis users have an onset of disease around 2 to 3 years earlier than non-users.

What is the prevalence of cannabis use in patients with psychotic illnesses?

We included three meta-analyses [30, 36, 40] that addressed this question. Myles et al. [36] (SIGN+, LoE4) analyzed 40 studies with 6321 participants. They reported an estimated prevalence of cannabis use in first-episode psychosis of 33.7% (95% CI 31–39%) based on 35 studies. The OR of continuing cannabis use after a first-episode psychosis was 0.56 (95% CI 0.40–0.79) based on 19 studies [36].

Sara et al. [40] (SIGN++, LoE4) investigated 64 studies with 22.500 participants. They found a pooled rate of stimulant use disorder of 8.9% (95% CI 7.4–10.5%) and that cannabis use disorders accounted for 43% of the between-study variance [40].

Koskinen et al. [30] (SIGN++, LoE4) included 25 studies with 5540 participants and showed that the median current rate of cannabis use disorders in schizophrenia patients was 16% (interquartile range = 8.6–28.6) in 10 studies. The median lifetime rate (based on 28 studies) was higher: 27.1% (interquartile range = 12.2–38.5). A comparison of patients with first-episode psychoses and long-term psychoses patients showed higher rates of current use (28.6% vs. 22.0%) as well as for lifetime use (44% vs. 12.2%) in first-episode patients. Cannabis use disorders were more common in younger patients (< 30 years) than in those over 30 years (current: 38.5% vs. 16.0%; lifetime 45.0% vs. 17.9%) [30]. In summary, these publications show that patients with psychotic disorders have a higher prevalence of cannabis use

and cannabis use disorders compared to the general population. However, there is some variation in the prevalence estimates that may reflect national differences in prevalence of cannabis use.

Are there differences between cannabis users and non-users in the symptomatology and the outcome of psychotic illnesses?

Our systematic search identified five meta-analyses [10, 29, 38, 39, 42] and three systematic reviews [43, 51, 53]. Schoeler et al. [10] (SIGN++, LoE1) conducted a meta-analysis of 24 studies with 16,565 subjects on whether the use or continued use of cannabis had an impact on relapses after the onset of psychosis. Cannabis users had a higher risk of relapse compared to non-users ($d = 0.36$, 95% CI 0.22–0.50). Continued use was associated with higher rates of relapses than non-use ($d = 0.31$, 95% CI 0.04–0.57) and discontinued use ($d = 0.28$, 95% CI 0.12–0.44). Non-users did not differ from discontinued users ($d = 0.02$, 95% CI −0.12 to 0.15). Continuous cannabis use was associated with a higher positive symptom severity ($d = 0.15$, 95% CI 0.01–0.29), but there was no impact on negative symptoms [10].

The systematic review by Zammit et al. [53] (SIGN++, LoE1) of 13 studies showed that cannabis use was associated with increased relapse rates (including re-hospitalization rates) and non-adherence. In seven studies increased positive symptoms were observed in cannabis users but this finding was inconsistent between studies. Other outcomes were less consistently associated with cannabis use [53].

Szoke et al. [42] (SIGN+, LoE3) performed a meta-analysis of 29 studies to explore the association between cannabis use and schizotypy. They found higher schizotypy scores in cannabis users (lifetime) than in never users for total, positive, negative and disorganizations scores (Hedges' $g = 0.18$–0.44). A similar pattern was found in the comparison of current cannabis users vs. those subjects who did not use cannabis, with higher scores on all dimensions (Hedges' $g = 0.10$–0.23) [42].

Baldacchino et al. [43] (SIGN++, LoE3) reviewed 13 studies to evaluate whether specific symptoms were related to cannabis-induced psychoses. Because of heterogeneity in the studies, the authors did not to perform a meta-analysis, but presented a qualitative analysis. They concluded that from a psychopathological perspective a separate cannabis-induced psychosis could not be identified [43].

The aim of the meta-analysis by Burns [29] (SIGN−, LoE4) was to identify the duration of untreated psychoses (DUP) in patients with first-episode psychoses who were using cannabis or not. A total of seven studies with 1453 first-episode patients (cannabis user and non-users) were included. No significant differences in the DUP were found between cannabis users vs. non-users (Hedges' g: −0.114, 95% CI −0.160 to 0.042) or between substance users vs. non-users (Hedges' $g = -0.038$, 95% CI −0.136 to 0.060) [29].

The systematic review of Serafini et al. [51] (SIGN+, LoE4) evaluated the relationship between cannabis use and suicidal behavior in patients with and without psychosis. Due to the heterogeneity of studies, the authors decided not to perform a meta-analysis. They were not able to detect a consistent association between suicidal behavior and cannabis-use in psychotic patients. Cannabis use seemed not to be a robust risk factor for suicidal attempts and behaviors in both psychotic and non-psychotic samples [51].

Potvin et al. (SIGN+, LoE4) published two overlapping meta-analyses [38, 39] that investigated the impact of dual diagnosis on depressive and negative symptoms in schizophrenia. Patients with dual diagnosis (cannabis, three studies) had more negative symptoms (Hedges' $g = -0.51$, 95% CI −0.76 to −0.25) [39], but did not differ in depressive symptoms (two studies) (Hedges' $g = 0.003$, 95% CI −0.361 to 0.366) [38].

In summary, these reviews show that cannabis use may worsen the course of psychotic disorders (e.g., positive symptoms, relapse rates, number of hospitalizations). However, some outcome domains (e.g., DUP, suicidality) did not differ between cannabis users and non-users.

Is there evidence for a biological link between the use of cannabis and the development of a psychotic illness?

We did not identify any meta-analysis that answered this research question. However, we found seven systematic reviews that assessed the impact of cannabis use on brain structure and integrity [45, 48–50] and on genetic/neurochemical outcome variables [46, 47, 52]. As detailed in Table 1, all included reviews apart from one [49] had a LoE4 limiting the presented results. None enabled conclusions to be drawn on the relationship of cannabis use to biological effects on the human brain and disease outcomes.

Malchow et al. [49] (SIGN+, LoE3) found that long-term use of cannabis was associated with changes in brain morphology in patients with schizophrenia but this could not be established in the early course of the illness. This result was limited by the small sample sizes and cross-sectional designs of the studies. Cookey et al. [45] (SIGN+, LoE4) addressed a related question in similarly limited study designs and found reduced white matter volumes in early schizophrenia that were more pronounced in cannabis users. Related results were reported by James et al. [48] (SIGN+, LoE4) but there was no clear relationship between cannabis use and the amount of volumetric changes. Rapp et al. [50] (SIGN++, LoE4) showed that cannabis use may result in brain volume

loss specifically in areas with a high density of CB1 receptors (cingulate, prefrontal cortex, and cerebellum).

Geoffroy et al. [47] (SIGN+, LoE4) investigated gene x environment interaction between cannabis use and genetic liability in impacts on cortical thickness and white matter volumes but the studies do not establish a causal relationship. Uliana et al. [52] (SIGN+, LoE4) were not able to clearly identify a certain genetic vulnerability for cannabis-induced psychosis, but suggested that AKT1 was a promising candidate gene. Finally, Ferretjans et al. [46] (SIGN+, LoE4) discussed whether increased cannabis use in persons with a hyperactive endocannabinoid system was associated with an increased risk of psychosis but results were not consistent across studies.

Overall, there was no clear relationship between psychosis, cannabis use and biological changes because of the small sample sizes in the studies included in the systematic reviews and the high heterogeneity of the findings.

Moderating variables

The qualitative analyses of the moderating variables age and gender were also part of the CaPRis study [20] and our review. In general, males have higher rates of cannabis use, abuse and dependency and thus more males than females with psychotic illness use cannabis. In the here-included publications no clear effect of gender could be observed. Some limited evidence is available that younger people with psychotic illness and cannabis use may be more affected than older patients [30]. Moreover, frequent use of cannabis in younger ages seems to be an additional risk factor for developing a psychotic illness [41]. However, apart from the above-described effect of cannabis use on earlier disease onset, no clear impact of age could be detected.

Discussion

We were able to show: (1) that psychotic illnesses occur more frequently in cannabis users than non-users, (2) that any lifetime cannabis use is associated with a 1.4 and cannabis dependence with a 3.4-fold increased risk of developing psychotic illness, and (3) that cannabis users have an earlier onset of psychoses than non-users. The literature also suggested: (1) that the use of cannabis was associated with increased relapse rates, more hospitalizations and more pronounced positive symptoms in psychotic patients; (2) that cannabis discontinuation reduces the risk of poor outcomes to levels comparable to that in patients who have never used cannabis; and (3) that cannabis use is more frequent in psychotic patients.

We were less confident about a number of other relationships because the evidence was inconsistent, or the necessary research had not been done. We could not detect any consistent evidence that cannabis use was associated with suicidality or DUP. Young persons (< 30 years) with psychosis did seem to have a particularly high risk of cannabis-related impairments but this needs to be confirmed. There was no clear evidence for an association between brain structure, cannabis use and the development and course of psychotic illness, reflecting an absence of adequately powered and rigorous studies to answer this question.

One systematic review of epidemiological studies [2] not included in our analyses due to methodological reasons supports our finding that cannabis use increases the risk of psychotic experiences and developing psychoses. The same group reported a bi-directional two-sample Mendelian randomization study that used summary-level genome-wide data from the International Cannabis Consortium and the Psychiatric Genomics Consortium. This showed "some evidence consistent with a causal effect of cannabis initiation on risk of schizophrenia [odds ratio (OR) 1.04 per doubling odds of cannabis initiation, 95% confidence interval (CI) 1.01–1.07, $p = 0.019$]". The study also found "strong evidence consistent with a causal effect of schizophrenia risk on likelihood of cannabis initiation (OR 1.10 per doubling of the odds of schizophrenia, 95% CI 1.05–1.14, $p = 2.64 \times 10^{-5}$)" [54]. However, the sample was limited to lifetime cannabis use rather than cannabis dependency possibly explaining the modest ORs.

The results of our review and these publications do not provide definite proof that cannabis or other environmental factors alone cause psychosis. However, they do provide consistent support for cannabis use being a contributory cause of psychosis and for continued cannabis use worsening the outcome of psychoses.

From a clinical perspective our results show that individuals seeking help with psychotic symptoms or diagnosed psychosis should be encouraged to stop using cannabis as recommended in various national and international schizophrenia guidelines [55–58]. Based on the available evidence one could conclude that it will be difficult to successfully treat these patients with psychosis without addressing their cannabis use. However, the challenge is that, there is a lack of strong evidence for the effectiveness of specific psychotherapeutic interventions in psychotic cannabis users [58, 59] in contrast to alcohol and tobacco use/abuse/dependency in psychosis [56, 58, 60].

Our results further indicate the need for awareness campaigns to inform young people about the risks of psychosis associated with the use of cannabis. These campaigns should stress: the increased risks of early initiation of use (i.e., use beginning in the mid-teens) and of daily and near daily cannabis use; and the probable increase in risks of this outcome among young people who have a personal or family history of serious psychiatric disorders. Moreover,

there would be a case for including information about the risks of psychosis in mandatory health warning messages for cannabis (much like those for alcohol and tobacco) in jurisdictions where cannabis can be purchased legally for medical and nonmedical use.

Our work has some limitations that need to be considered. First, from our findings a causal relationship between cannabis use/abuse and the onset or worsening of psychoses cannot be concluded. Interestingly, after the finalization of our literature search, a Danish register-based cohort study including 204,505 individuals diagnosed with substance abuse and 21,305 diagnosed with schizophrenia reported that cannabis (HR 5.20, 95% CI 4.86–5.57) and alcohol (HR 3.38, 95% CI 3.24–3.53) have the strongest associations for a conversion from a substance abuse disorder to schizophrenia [61]. From the same group, a recent publication indicates that also substance abuse disorders are associated with a transition from schizotypal disorder to schizophrenia with a conversion rate of 33.1% (95% CI 29.3–37.3%) for all drugs and 58.2% (95% CI 44.8–72.2%) for patients with cannabis use disorders [62]. These findings support our line of argument. Second, we did not perform a meta-analysis. Thus, our results are of a qualitative nature and cannot be considered as a source for aggregated evidence. Third, our findings do not provide any information on protective factors associated with safe ways of using cannabis not to reduce the risk of developing psychosis or schizophrenia (e.g., ensuring a high ratio of CBD-to-THC). Finally, our findings could not address all aspects of this important topic.

We see the urgent need for the following types of research: (1) more longitudinal studies that control for important confounding variables [e.g., age of onset of cannabis use, effects of other drugs, effects of other environmental factors (e.g., migration, trauma)] to better characterize the relationship between cannabis use and development of psychoses; (2) randomized controlled clinical trials of the effectiveness of interventions to cease cannabis use in patients with psychosis who use cannabis; (3) research on the doses of THC and frequency of cannabis use among people with psychoses; (4) research on the reverse causality hypothesis [63]; (5) research on the changing cannabinoid composition of cannabis [59], such as the proportions of THC and cannabidiol (CBD) [59] and the impact of THC/CBD ratio on risk of developing psychoses in light of suggestive findings that the increased THC content of cannabis has increased its potential to induce psychosis [59].

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Compliance with ethical standards

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