

Mini-CAT Draft

Name: Jay Kolasinac

A 25yo, caucasian male, unemployed, domiciled, w/ no significant PMH or PPH, was BIBEMS activated by mother, for bizarre behavior. The mother stated the son was talking to himself and stated he told her that he was hearing voices. He was acting very bizarre. The patient does not take any medication nor does he drink alcohol. The patient admits to smoking marijuana on a regular basis ever since graduating high school about 7 years ago. He denies suicidal ideation/homicidal ideation.

Search Question: In cannabis users, does smoking cannabis predispose a patient to early onset psychosis?

Question Type: What kind of question is this? (boxes now checkable in Word)

- Prevalence Screening Diagnosis
- Prognosis Treatment Harms

Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)?

Please explain your choices.

Along with meta-analyses and systematic reviews, I believe observational studies would also be types of studies I might want to include. The subject of interests, cannabis users, would be observed for specific risk factors [cannabis use] or for specific outcomes [early onset psychosis].

PICO search terms:

P	I	C	O
Cannabis users	Smoking cannabis	None	Early onset psychosis
Marijuana users	Smoking marijuana		First-time episode of psychosis
			Psychiatric disorders

Search tools and strategy used:

Database	Terms	Filter	# of Articles
PubMed	((cannabis users) OR marijuana users) AND early onset psychosis	Medline, last 5 years	926
ScienceDirect	((cannabis users) OR marijuana users) AND early onset psychosis	Research articles, last 5 years, Psychology	172

I narrowed my search articles by including filters [Medline, last 5 years, research articles, etc]. I wanted high level of evidence articles so I aimed meta-analyses or systematic reviews where I was able to find a few that focused on my PICO question and applied to all my filters.

Results found:

Article 1

Citation

Myles, H., Myles, N., & Large, M. (2015). *Cannabis use in first episode psychosis: Meta-analysis of prevalence, and the time course of initiation and continued use. Australian & New Zealand Journal of Psychiatry, 50(3), 208–219.* doi:10.1177/0004867415599846

[sci-hub.se/10.1177/0004867415599846](https://doi.org/10.1177/0004867415599846)

Article Type

Meta-analysis

Abstract

Objectives: Cannabis use is prevalent among people with first episode psychosis and the epidemiology of its use in early psychosis is unclear. We performed a meta-analysis of observational studies to determine; (1) the interval between age at initiation of cannabis use and age at onset of first episode psychosis, (2) the prevalence of cannabis use at time of first episode psychosis, and (3) the odds of continuing cannabis following treatment for first episode psychosis.

Data sources: Search of electronic databases MEDLINE, EMBASE, PsycINFO, Web of Science and CINAHL for Englishlanguage papers using search terms (psychosis OR schizophrenia) AND (cannabis OR marijuana) IN (title OR keyword OR abstract), current to October 2014.

Study selection: Studies were included if they reported on prevalence of current cannabis use in first episode psychosis cohorts. A total of 37 samples were included for meta-analysis.

Data extraction: Rates of cannabis use in each sample were extracted to determine prevalence estimates. The age at initiation of regular cannabis and age at onset of psychosis were used to determine the length of cannabis use preceding psychosis. Prevalence estimates at first episode psychosis and various time points of follow-up following first episode psychosis were analysed to determine odds ratio of continuing cannabis use. Data synthesis was performed using random-effects meta-analyses.

Results: The pooled estimate for the interval between initiation of regular cannabis use and age at onset of psychosis was 6.3years (10 samples, standardised mean difference=1.56, 95% confidence interval=[1.40, 1.72]). The estimated prevalence of cannabis use at first episode psychosis was 33.7% (35 samples, 95% confidence interval=[31%, 39%]). Odds of continued cannabis use between 6months and 10 years following first episode psychosis was 0.56 (19 samples, 95% confidence interval=[0.40, 0.79]).

Article 2

Citation

Bagot, K. S., Milin, R., & Kaminer, Y. (2015). *Adolescent Initiation of Cannabis Use and Early-Onset Psychosis*. *Substance Abuse*, 36(4), 524–533. doi:10.1080/08897077.2014.995332

sci-hub.se/10.1080/08897077.2014.995332

Article Type

Systematic review

Abstract

Background: It is important to evaluate the impact of cannabis use on onset and course of psychotic illness, as the increasing number of novice cannabis users may translate into a greater public health burden. This study aims to examine the relationship between adolescent onset of regular marijuana use and age of onset of prodromal symptoms, or first episode psychosis, and the manifestation of psychotic symptoms in those adolescents who use cannabis regularly.

Methods: A review was conducted of the current literature for youth who initiated cannabis use prior to the age of 18 and experienced psychotic symptoms at, or prior to, the age of 25. Seventeen studies met eligibility criteria and were included in this review.

Results: The current weight of evidence supports the hypothesis that early initiation of cannabis use increases the risk of early onset psychotic disorder, especially for those with a preexisting vulnerability and who have greater severity of use. There is also a dose-response association between cannabis use and symptoms, such that those who use more tend to experience greater number and severity of prodromal and diagnostic psychotic symptoms. Those with early-onset psychotic disorder and comorbid cannabis use show a poorer course of illness in regards to psychotic symptoms, treatment, and functional outcomes. However, those with early initiation of cannabis use appear to show a higher level of social functioning than non-cannabis users.

Conclusions: Adolescent initiation of cannabis use is associated, in a dose-dependent fashion, with emergence and severity of psychotic symptoms and functional impairment such that those who initiate use earlier and use at higher frequencies demonstrate poorer illness and treatment outcomes. These associations appear more robust for adolescents at high risk for developing a psychotic disorder.

Article 3

Citation

van der Steur SJ, Batalla A, Bossong MG. Factors Moderating the Association Between Cannabis Use and Psychosis Risk: A Systematic Review. *Brain Sci.* 2020;10(2):97. Published 2020 Feb 12. doi:10.3390/brainsci10020097

[sci-hub.se/10.3390/brainsci10020097](https://doi.org/10.3390/brainsci10020097)

Article Type

Systematic review

Abstract

Increasing evidence indicates a relationship between cannabis use and psychosis risk. Specific factors, such as determinants of cannabis use or the genetic profile of cannabis users, appear to moderate this association. The present systematic review presents a detailed and up-to-date literature overview on factors that influence the relationship between cannabis use and psychosis risk. A systematic search was performed according to the PRISMA guidelines in MEDLINE and Embase, and 56 studies were included. The results show that, in particular, frequent cannabis use, especially daily use, and the consumption of high-potency cannabis are associated with a higher risk of developing psychosis. Moreover, several genotypes moderate the impact of cannabis use on psychosis risk, particularly those involved in the dopamine function, such as AKT1. Finally, cannabis use is associated with an earlier psychosis onset and increased risk of transition in individuals at a clinical high risk of psychosis. These findings indicate that changing cannabis use behavior could be a harm reduction strategy employed to lower the risk of developing psychosis. Future

research should aim to further develop specific biomarkers and genetic profiles for psychosis, thereby contributing to the identification of individuals at the highest risk of developing a psychotic disorder.

Article 4

Citation

Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M., & Vassos, E. (2016). *Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis*. *Schizophrenia Bulletin*, 42(5), 1262–1269. doi:10.1093/schbul/sbw003

<https://sci-hub.se/https://dx.doi.org/10.1093%2Fschbul%2Fsbw003#>

Article Type

Meta-analysis

Abstract

Cannabis use has been reported to induce long-lasting psychotic disorders and a dose-response relationship has been observed. We performed a systematic review of studies that investigate the association between the degree of cannabis consumption and psychosis and a meta-analysis to quantify the magnitude of effect. Published studies were identified through search of electronic databases, supplemented by manual searches of bibliographies. Studies were considered if they provided data on cannabis consumption prior to the onset of psychosis using a dose criterion (frequency/ amount used) and reported psychosis-related outcomes. We performed random effects meta-analysis of individual data points generated with a simulation method from the summary data of the original studies. From 571 references, 18 studies fulfilled inclusion criteria for the systematic review and 10 were inserted in the meta-analysis, enrolling a total of 66 816 individuals. Higher levels of cannabis use were associated with increased risk for psychosis in all the included studies. A logistic regression model gave an OR of 3.90 (95% CI 2.84 to 5.34) for the risk of schizophrenia and other psychosis-related outcomes among the heaviest cannabis users compared to the nonusers. Current evidence shows that high levels of cannabis use increase the risk of psychotic outcomes and confirms a dose-response relationship between the level of use and the risk for psychosis. Although a causal link cannot be unequivocally established, there is sufficient evidence to justify harm reduction prevention programs.

Summary of the Evidence:

Author (Date)	Level of Evidence	Sample/Setting (# of subjects/ studies, cohort definition etc.)	Outcome(s) studied	Key Findings	Limitations and Biases
Myles, H., Myles, N., & Large, M. (2015).	Meta-analysis	<p>-Studies were included if they reported on prevalence of current cannabis use in first episode psychosis cohorts.</p> <p>-A total of 37 samples were included for meta-analysis.</p> <p>-796 subjects for initiation -6321 subjects for prevalence -3645 subjects for continuation</p>	<p>- The interval between age at initiation of cannabis use and age at onset of first episode psychosis</p> <p>-The prevalence of cannabis use at time of first episode psychosis</p> <p>-The odds of continuing cannabis following treatment for first episode psychosis</p>	<p>- The pooled estimate for the interval between initiation of regular cannabis use and age at onset of psychosis was 6.3years</p> <p>- The estimated prevalence of cannabis use at first episode psychosis was 33.7%</p> <p>- This analysis indicates cannabis use predates and is prevalent in early psychosis</p>	<p>-Only observational studies were included in the meta-analysis</p> <p>- That cannabis use by people with psychosis is likely to also be impacted by complex social and geographical factors.</p>
Bagot, K. S., Milin, R., & Kaminer, Y. (2015).	Systematic review	<p>-Searched all relevant literature between 1967 and 2014</p> <p>-17 articles were included</p>	<p>- To evaluate the impact of cannabis use on onset and course of psychotic illness, as the increasing number of novice cannabis users may translate into a greater public health burden</p>	<p>-Usage of cannabis is associated with emergence and severity of psychotic symptoms and functional impairments.</p> <p>-More robust association noted with cannabis usage and those who</p>	<p>- 2 studies had small sample sizes, thus limiting the power and ability to detect small to</p>

			<ul style="list-style-type: none"> - To examine the relationship between adolescent onset of regular marijuana use and age of onset of prodromal symptoms, or first episode psychosis, and the manifestation of psychotic symptoms in those adolescents who use cannabis regularly 	<p>are deemed high risk for psychotic disorders</p> <ul style="list-style-type: none"> -The data presented here appears to validate the independent association between early cannabis usage and early-onset first-episode psychosis 	<p>medium effects</p> <ul style="list-style-type: none"> - Also, several studies did not control for confounding factors such as polysubstance abuse and did not differentiate between CU alone and polysubstance abuse
van der Steur SJ, Batalla A, Bossong MG.(2020)	Systematic review	<ul style="list-style-type: none"> -56 studies were included in the review -Human studies between 2009 and 2019 	<ul style="list-style-type: none"> -Patterns of cannabis use (e.g., dose and frequency); -Age of initiation of cannabis use; -Type of cannabis used; and -The individual genetic profile. 	<ul style="list-style-type: none"> -Use of cannabis increases the risk of psychosis -Cannabis use lowers the age of onset of psychosis by 3 years and increases the risk of transition in subjects who are already high risk for psychotic disorders - Several genotypes have been shown to moderate the impact of cannabis use on psychosis risk, particularly those involved in the dopamine function, such as AKT1. 	<ul style="list-style-type: none"> -Not all of the studies included focused primarily on the same topic. Some articles chosen focused more on linking cannabis to psychosis while others focused on genetic

					factors that may have played a role, etc.
Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M., & Vassos, E. (2016).	Meta-analysis	- From 571 references, 18 studies fulfilled inclusion criteria for the systematic review and 10 were inserted in the meta-analysis, enrolling a total of 66 816 individuals.	-Investigate the association between the degree of cannabis consumption and psychosis and a meta-analysis to quantify the magnitude of effect.	-Current evidence shows that high levels of cannabis use increase the risk of psychotic outcomes and confirms a dose-response relationship between the level of use and the risk for psychosis. -Although a causal link cannot be unequivocally established, there is sufficient evidence to justify harm reduction prevention programs.	-Examining both “soft” outcomes such as psychotic experiences and “hard” outcomes such as diagnosis or admission with a psychotic disorder -They did not have data on the time interval between regular cannabis use to illness onset. -Included dissimilar study designs ranging from

					general population cohorts to cross-sectional studies of cases and controls with retrospective measurement of cannabis use.
--	--	--	--	--	---

Conclusions:

1. Myles et al., concluded that cannabis use predates and is prevalent in early psychosis. Warrants further research as legalization across US seems very possible.
2. Bagot et al., concluded that cannabis usage was associated with increased emergence and severity in psychotic episodes. More robust outcomes are seen in individuals who are already at high risk of developing some type of psychotic disorder.
3. van der Steur et al., concluded that usage of cannabis increases the risk of psychosis. They also concluded that cannabis usage lowers the age of onset of first episode psychosis by 3 years and increases risk of transition in subjects who are already high for psychotic disorders.
4. Marconi, A et al., concluded that high levels of cannabis use increases the risk of psychotic outcomes. There is a dose related relationship between the level of usage and with the risk of psychosis.

Overarching conclusion:

The development of early onset psychosis is seen in individuals who smoke marijuana/cannabis. Those who are clinically at high risk for development of psychiatric disorders already tend to see more pronounced outcomes of psychosis.

Clinical Bottom Line:

The clinical bottom line from all three of the selected articles is that the usage cannabis ultimately predisposes a patient to an earlier age of onset for psychosis. Myles et al., concluded that cannabis use predates and is prevalent in early psychosis. Bagot et al., concluded that cannabis usage was associated with increased emergence and severity in psychotic episodes. The association was more profound in individuals who were already seen as high risk for psychotic disorders. van der Steur et al., the most recent of the 3 studies, concluded that cannabis can lower the age of onset of psychosis by as much as 3 years. Based on the evidence, we could conclude there is an association between cannabis and early-onset psychosis. With the motion to legalize cannabis across the US, we could see an increase in prevalence of early onset psychosis. Future/current studies need to be conducted to further explore this hypothesis. Now that efforts are made to further legalize cannabis, what can be done to inform the public of the dangers of marijuana, especially to those who are already at high risk for psychosis?

Weight of Evidence:

1. This article was a meta-analysis, which utilized 37 different samples and was published within the last 5 years. The entire analysis was not focused primarily on onset of psychosis and cannabis usage, it also focused on the age of initiation of cannabis and the odds of continuing cannabis post psychosis.
2. This was a systematic review that included 17 articles in its review. The review was conducted within the last 5 years and answered my PICO question directly. It focused directly on cannabis usage and early onset psychosis.
3. This article was a systematic review that was recently published last year. It is the most recent of the four article and included 56 studies in the review. The article did not focus primarily on one aspect of cannabis usage and psychosis development but rather many different topics. Not all of the 56 studies pertained to my question.
4. This article was a meta-analysis and included 66,816 subjects within the analysis. The article was published with in the last 5 years but did not include many RCTs which lowers weight in evidence.

Magnitude of Effects:

1. Meta-analysis of initiation found that regular cannabis use begins at 6.3 years before age at onset of psychosis (SMD=1.56, 95% confidence interval [CI]=[1.40, 1.72]; Heterogeneity was moderate and statistically significant

- ($Q=17.85$, $df(Q)=9$, $p=0.04$, $I^2=49.6$). Meta-analysis of prevalence indicated 33.7% (95% CI=[29%, 38%]) of subjects used cannabis at the time of first episode psychosis
2. Those who initiate CU by age 15 and age 18 demonstrate more symptoms of Schizophrenia by age 26 as compared with neverusers.¹⁹ A noteworthy study has shown that as the duration of CU increases from first use (6 years), the odds of development of a nonaffective psychosis increase (adjusted OR [aOR] D 2.2), as well as number/severity of delusions (aOR D 4.3) and hallucinations (aOR D 2.8).³⁸ These associations held true for sibling pairs, decreasing the likelihood that unmeasured confounding factors affected outcomes.
 3. In a cohort study of 1756 adolescents, Gage et al. (2014) investigated cannabis use at age 16 in relation to the emergence of psychotic experiences at age 18 and found that frequent cannabis use increased the odds of psychotic experiences (OR = 1.48, 95% CI 1.18–1.86, P = 0.001).
 4. Used a random effect model for the meta-analysis, due to the high heterogeneity of the studies ($I^2 = 82\%$). The pooled estimate for the logistic regression coefficient b was 1.36 (95% CI: 1.04 to 1.68), corresponding to an OR of 3.90 (2.84 to 5.34) for the risk of schizophrenia and other psychosis outcomes among the most severe cannabis users compared to the nonusers

Clinical Significance:

As cannabis begins to legalize across the United States, we can safely assume the prevalence of early-onset psychosis due to cannabis usage will increase in the coming years. Especially in the psychiatric emergency room setting, if patients present with first time psychosis, a good question to ask would be if the patient had any previous drug usage. Now a days, individuals tend not to consider marijuana as a “drug” the same way many Americans do not consider alcohol or tobacco as drugs. Clinicians should inquire specifically about marijuana usage [frequency, dosage, dose, etc] to help in diagnosis of marijuana induced substance disorder vs other psychiatric conditions.

Any other considerations:

Now that efforts are made to further legalize cannabis, what can be done to inform the public of the dangers of marijuana, especially to those who are already at high risk for psychosis? Studies need to be performed to better understand the biological pathway that link cannabis usage to onset of psychosis in cannabis users. Based on this evidence, there should be educational programs to educate cannabis users about potentially developing psychosis while using the drug, especially in individuals who are already at risk for developing psychosis.