CANNABIS USE AND SUICIDE IN NON-AFFECTIVE PSYCHOSIS: A MINI-REVIEW OF RECENT LITERATURE

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Summary

Proof of correlation between psychotic spectrum disorders and suicide are found in literature, as well as between cannabis use disorder (CUD) and suicide and between CUD and schizophrenia. The study population of the selected papers consists of subjects diagnosed with schizophrenia spectrum or cannabis or SCs induced psychosis. Our objective is to assess how suicide risk (defined as suicidal ideation/attempt or death by suicide) in this population may vary with exposure to cannabis or one of its main active compounds. We searched PubMed, Scopus and Psycinfo database from January 2010 to February 2022. Study designs of the included articles are distributed as follows: 6 cross-sectional studies, 3 cohort studies, 1 case-control studies, 1 randomized double-blind study, 1 case report. Selected cohort studies seem to agree in identifying an increased suicide risk in patients with schizophrenia spectrum disorders when exposed to cannabis use.

The case-control study and selected cross-sectionals provide contradictory data. However, qualitative analysis seem to point toward a positive correlation between cannabis use and increased suicidal risk in patients with schizophrenia spectrum disorders. In conclusion, emerging data on the correlation between cannabis use and suicide risk in patients with schizophrenia or other schizophrenic spectrum disorders are insufficient to draw firm conclusions. Nonetheless these studies seem to suggest a positive correlation of cannabis use with increased suicide risk, particularly regarding first episode psychosis (FEP) and male gender. Clinicians should be aware of the possibility of a higher risk of suicidal behavior associated specifically with cannabis use for men and patients during FEP.

Keywords: cannabis, schizophrenia, non-affective psychosis, suicide, suicide risk, first episode psychosis

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INTRODUCTION

Compared to the general population, schizophrenic patients have and increased risk of suicide (Barbeito et al. 2021, Castelein et al. 2015, Yin et al. 2020; Fantegrossi et al. 2014). Patients appear particularly vulnerable during the first psychotic episode (FEP) (Pelizza et al. 2021), especially with regards to male patients(Sicotte et al. 2021). Some studies have identified risk factors associated with an increased susceptibility of suicide in psychotic patients: social problem solving (Breitborde et al. 2021a, 2021b; Deep et al. 2018), sleep disorders (Miller et al. 2019), reduced cognitive functions (Canal-Rivero et al. 2018), and depressive symptoms during FEP (Bornheimer et al. 2021).

There is also a strong interdependency between schizophrenia and substance abuse disorder (SAD), in particularly cannabis (Patel et al. 2020). Not only cannabis use disorder (CUD) and synthetic cannabinoids (SCs) seem to be a possible risk factor for the development of a psychotic disorder, but also are likely to be involved in the progression of the disease as well as determining the severity of symptoms (Ricci et al. 2021, Papanti et al. 2013) Indeed, cannabis use is considered a preventable risk factor for psychosis. The association between cannabis use and nonaffective psychotic pathology appears to be stronger in cases of early age use (Arseneault et al. 2002) or in the case of consumption of cannabis with a high concentration of THC (Di Forti et al. 2015, Di Forti et al. 2009). On the other hand, patients with schizophrenia have an increased risk of developing a substance use disorder (McGinty et al. 2018, Large et al. 2011). In fact, the rate of cannabis dependence is disproportionately high among people with psychosis and may be related to the underlying neurobiology of the disorder (Galletly et al. 2016).

Cannabis contains more than 80 cannabinoids. These are chemicals of natural origin that interact with the receptors of the endocannabinoid system. Among these, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the ones present in greater quantities. THC, the

main psychoactive component of Natural Cannabis (NC), is a partial agonist of the cannabinoid receptors CB1 and CB2 and it is believed to be responsible for the risk of developing psychotic symptoms (Iseger & Bossong, 2015). CBD has little binding affinity to cannabinoid receptors and it carries antipsychotic and anxiolytic properties (Iseger & Bossong, 2015). Over the last decade, several studies have reported that cannabis strains with a higher ratio of THC, such as SCs have a stronger association with the risk of developing psychotic disorders (Di Forti et al. 2015).

Several articles emerge from the literature showing a link between chronic cannabis use and suicidal ideation and attempts (Di Forti et al. 2009, Fenton 2000; Hirvonen et al. 2012) particularly if consumed at a young age (14-15 years old) (Gobbi et al. 2019). Some studies suggest that a dysregulation of the cannabinoid system (up-regulation of the CB1 receptor) is associated with an increased risk of suicide, implying that THC may be implicated in altering this system (Mannekote et al. 2021).

Given the link between schizophrenia and suicide, cannabis and suicide, cannabis and schizophrenia, and since some of the most relevant risk factors for suicide in schizophrenia patients may be influenced by cannabis use, we decided to conduct a literature search.

Our study population consists of subjects diagnosed with schizophrenia spectrum or cannabis or SCs induced psychosis. The objective of this study is to investigate whether or not this population when exposed to cannabis use shows an increased suicidal risk (understood as increased suicidal ideation, suicide attempt or death by suicide) compared to the corresponding population not using the same substance; as well as explaining and evaluating the nature and characteristics of this potential relation.

SUBJECTS AND METHODS

Search engines "PubMed" AND "Psycinfo" and "Scopus" were searched using specific search terms from January 2010 to February 2022. Out of 229 articles that came up, we selected 12 articles based on pre-determined inclusion and exclusion criteria. Selected articles were analysed and discussed in the departmental meeting. In carrying out this review, the PRISMA statement (Page et al. 2020) was followed. Finally, the quality the selected studies was assessed with the Newcastle-Ottawa quality assessment scale (Wells et al. 2013).

Eligibility criteria

For our review, we focused on studies involving patients with the following characteristics: 1) diagnosed with schizophrenic spectrum disorders or diagnosed with cannabis or SCs induced non-affective psychotic disorder; 2) current or past use of cannabinoids or SCs or other cannabis components; 3) presence of suicidal ideation/ attempt or death by suicide (we will use the expression 'suicide risk' to refer to these three scenarios); 4) only reports written in English. Specifically, we included all articles that reported on the effects of cannabis and synthetic cannabinoids (Fattore et al. 2016). In particular, considering that cannabis is a plant that contains multiple psychoactive components(Cohen et al. 2019), we chose to consider also the studies that reported the effects of the two main components: THC and CBD. Case reports have also been included in order to provide a complete overview of the literature.

We applied the following exclusion criteria: 1) articles in which were reported self-injurious acts without suicidal intent; 2) articles in which patients were not diagnosed with schizophrenia or schizophrenic spectrum disorders or were not diagnosed with non-affective psychotic disorder induced after using SCs; 3) articles that did not include specifically cannabinoids use but included drug abuse as a general category.

RESULTS

The research yielded a total of 88 articles on Pubmed database, 181 articles on Scopus database and 60 articles on Psycinfo, among which 137 overlapped. The remaining 229 papers have been screened to exclude other 31 articles represented by reviews or study designs that were not suitable for the purpose of this article, such as editorials and commentaries. In this group also articles whose full text was not available are included. The following process consisted in discarding 72 papers whose subject of matter utterly diverged from the search topic and 62 more articles whose field of study was not consonant with the aim of this review. A further screening, executed through the application of the exclusion criteria, resulted in the rejection of 52 studies. Eventually, 12 studies published between 2010 and 2021 were eligible for inclusion. The detailed process is described in fig. 1 flow-chart.

The results have been summarized in Tables "1", "2", "3".

Table 1: Main findings and study designs pt.1/3. Three cross sectional studies and a restrospective case-control study are here displayed. Half articles showed presence of a correlation between cannabis use and suicidal risk in psychosis, one in a positive and the other in negative sense, while this link was denied in the remaining articles.

Study title	Authors and journal	Study design	Sample	Diagnosis Criteria	Cannabis use evaluation	Suicide risk evaluation	Main findings	Limitations
Is cannabis a risk factor for suicide attempts in men and women with psychotic illness?	A. Waterreus et al. 2018 Journal of Psychopharmacology	Cross-sectional	1790 subjects M: 59,5%; F: 40,5% age: 18-64 y.o.	Non-affective psychosis according to ICD 10	Self-reported information about the past 12 months; patients divided into "daily users", "casual users" and "non-users"	Suicidal attempts/ ideas in the previous 12 months through SMHWB (National Survey of Mental Health and Wellbeing)	Positive correlation between cannabis consumption and rate of suicidal attempts in older males (>35 y.o.), negative correlation in younger males (<35 y.o.)	Cannabis use and suicidal attempts before the last 12 months are not considered. Cross-sectional data collection. Lack of objective data on current use of cannabis.
Significant relationship between lifetime alcohol use disorders and suicide attempts in an Australian schizophrenia sample.	D. McLean et al. 2012 Australian & New Zealand Journal of Psychiatry	Cross-sectional	821 subjects 167 first-degree related individuals contained within 79 indipendent families; M: 71%, F: 29%; age > 18 y.o.	93% schizophrenia 7% schizo-affective disorder according to DSM IV	DIGS (Diagnostic Interview for Genetic Studies) and FIGS (Family Interview for Genetic Studies)	Frequency of any suicide attempt	No correlation	Sample not representative of non-affective psychotic population (related patients, originally recruited for genetic studies). Cross-sectional data collection.
Differential effects of childhood trauma and cannabis use disorders in patients suffering from schizophrenia.	G. Baudin et al. 2016 Schizophrenia Research	Cross-sectional	366 subjects M: 74.86%, F: 23.14% age: 15-84 y.o. Selected on referral from psychiatrists or general practitioners.	Schizophrenia or schizo-affective disorder according to DSM IV	SCID-I	Columbia-Suicide Severity Rating Scale (C-SSRS).	No correlation	Cross-sectional data collection.
Psychopharmacological comparison of schizophrenia spectrum disorder with and without cannabis dependency.	Z. Makkos et al. 2011 Progress in Neuro-Psycho-pharmacology & Biological Psychiatry	Retrospective case-control	85 first-timed hospitalized patients age < 35 y.o.	Schizophrenia spectrum disorder according to DSM IV	Self-reported information	Frequency of any suicide attempt	Negative correlation between cannabis consumption and suicide attempts rates (higher in non-users group)	Age and gender distribution is different between the two groups (substance-using group younger and mostly males). Lack of objective data on current use of cannabis.

Table 2: Main findings and study designs pt.2/3. Three cohort studies and a cross-sectional study are here displayed. All articles confirmed the presence of a positive correlation between cannabis use and suicidal risk in psychosis, despite only partially in one of the works presented.

Study title	Authors and Journal	Study design	Sample	Diagnosis criteria	Cannabis use evaluation	Suicide risk evaluation	Main findings	Limitations
Morbidity and mortality in schizophrenia with comorbid substance use disorders.	M. Lähteenvuo et al. 2021; Acta psychiatrica scandinavica	Longitudinal Cohort	45.476 subjects from Finland and Sweden. Finnish SUD group: M: 71.9% F: 28.1% age <46 y.o. at cohort entry mean age: 32.9 y.o.	Schizophrenia according to ICD 10	Diagnosed SUD according to ICD 10 collected in register; complete suicides in the nationwide treatment register Cause of Death Register	Suicide attempts in treatment register; complete suicides in the Cause of Death Register	Partial correlation between cannabis consumption and rates of suicidal attempts (positive correlation in the Finnish cohort, no correlation in the Swedish cohort)	Results difficult to generalize (only to countries with similar Health Care Systems); only registered suicidal behaviors and diagnosed SUD are considered with risk for underestimation
Attempted Suicide in a Xhosa Schizophrenia and Schizoaffective Disorder Population.	M. Luckhoff et al. 2013; The official journal of the american association of suicidology	Cross-sectional	974 subjects M: 80.5% F: 19,5% mean age: 35 y.o.	Schizophrenia or schizoaffective disorders according to DSM IV	DIGS (at least 21 time/year)	DIGS	Positive correlation between cannabis consumption and suicide attempts	Only Xhosa population involved and prevalence of male.
Associations between substance use disorders and suicide or suicide attempts in people with mental illness.	M. LD Østergaard et al. 2017; Addiction	Cohort	-35.625 subjects -mean age: 27 – 33 y.o. -13-56 y.o.	Psychotic spectrum disorder according to ICD 10	Diagnosed SUD in hospital treatment register	Suicide attempts in treatment register; complete suicides in the Cause of Death Register	Positive correlation between cannabis consumption and rates of suicide attempts	Only diagnosed SUD and suicide attempts which caused hospitalization are considered (risk for understimation)
Suicidal behavior in first-episode nonaffective psychosis: Specific risk periods and stage-related factors.	R. Ayesa-Arriola et al. 2015; European Neuropsychopharmacology	Longitudinal Cohort	397 subjects M: 56,9%; F: 43,1% average age: 28,94 y.o.	Psychotic spectrum disorders (schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder, psychosis NOS and delusional disorder) according to DSM IV	Self-reported data ("yes or no" questionnaire)	Medical records. Patients divided into: - "Early attempters" (within 2 months from FEP) - "Late attempters" (beyond 2 months from FEP)	Positive and strong correlation (p=0.043) between cannabis consumption and suicidal risk especially in "late attempters"	Data about suicidal behaviour collected through medical records with risk for underestimation (some suicide deaths could occur before first contact with hospital); Cannabis use evaluation method not specified; Other suicide-related variables not considered

Table 3: Main findings and study designs pt.3/3. Two cross sectional studies, a case report and a case-control study are here displayed. Almost every article showed presence of a positive correlation between cannabis use and suicidal risk in psychosis, except for one work which denied any link.

Study title	Authors and Journal	Study design	Sample	Diagnosis criteria	Cannabis use evaluation	Suicide risk evaluation	Main findings	Limitations
Persistent cannabis use among young adults with early psychosis receiving coordinated specialty care in the United States	L. Marino et al. 2020 Schizophrenia Research	Cross-sectional	938 subjects M: 74%; F: 26% age: 16-30 y.o.	Standardized hospital admission forms	Clinician-reported data. Patients divided into "No use" "Reduced use"(use on admission and discontinued) "Persistent use" (use from admission continued during follow-up or use started during follow-up)	Physician and self-reported data regarding suicidal ideation, behaviour or attempts within 90 days prior to admission	Positive and strong correlation between cannabis consumption (especially persistent use) and increase of suicidal ideation or behaviour (p=0.045)	Impossible to stratify the risk depending on reduced or persistent drug use (lacking information about cannabis use frequency and transversal nature of the study)
Clinical characteristics of synthetic cannabinoid-induced psychosis in relation to schizophrenia: a single-center cross-sectional analysis of concurrently hospitalized patients.	M. Altintas et al. 2016 Neuropsychiatric Disease and Treatment	Cross-sectional	81 subjects M: 100% age 16 – 60 y.o.	50 subjects with SC-induced psychosis (symptoms and self-reported use for at least 4 months and no previous psychiatric diagnosis); 31 subjects with schizophrenia according to DSM- V criteria	Self-reported data	Rates of suicide attempts and ideation reported	Positive correlation between synthetic cannabis consumption and suicide risk	SC abuse investigated through anamnesis and not objective urinal analysis (all resulted negative). Lack of objective data on current use of cannabis.
Synthetic Cannabis Analogues and Suicidal Behavior: Case Report.	P.M. dos Santos Oliveira et al. 2017 Journal of Addiction Medicine	Case report	1 male Age 32 y.o.	Not specified	Self-reported data	Clinical presentation at hospital access	Positive correlation between synthetic cannabis consumption and suicidal risk	Case report (results are difficult to generalize) Diagnosis criteria not specified. Lack of objective data on current use of cannabis.
The effects of cannabidiol (CBD) on cognition and the other symptoms in outpatients with chronic schizophrenia: a randomized placebo-controlled trial.	D. L. Boggs et al. 2018 Journal of Psychopharmacology	Randomized placebo-controlled double-blind study	39 subjects age: 18 – 65 y. o.	Schizophrenia according to DSM-IV	CBD 600 mg/die administered for the study purpose in the case group of the trial	Clinical observation for increase of suicide risk as adverse effect	No correlation	Higher doses of CBD could have been tested (it has a low oral bioavailability and higher doses have been proven to be tolerated)
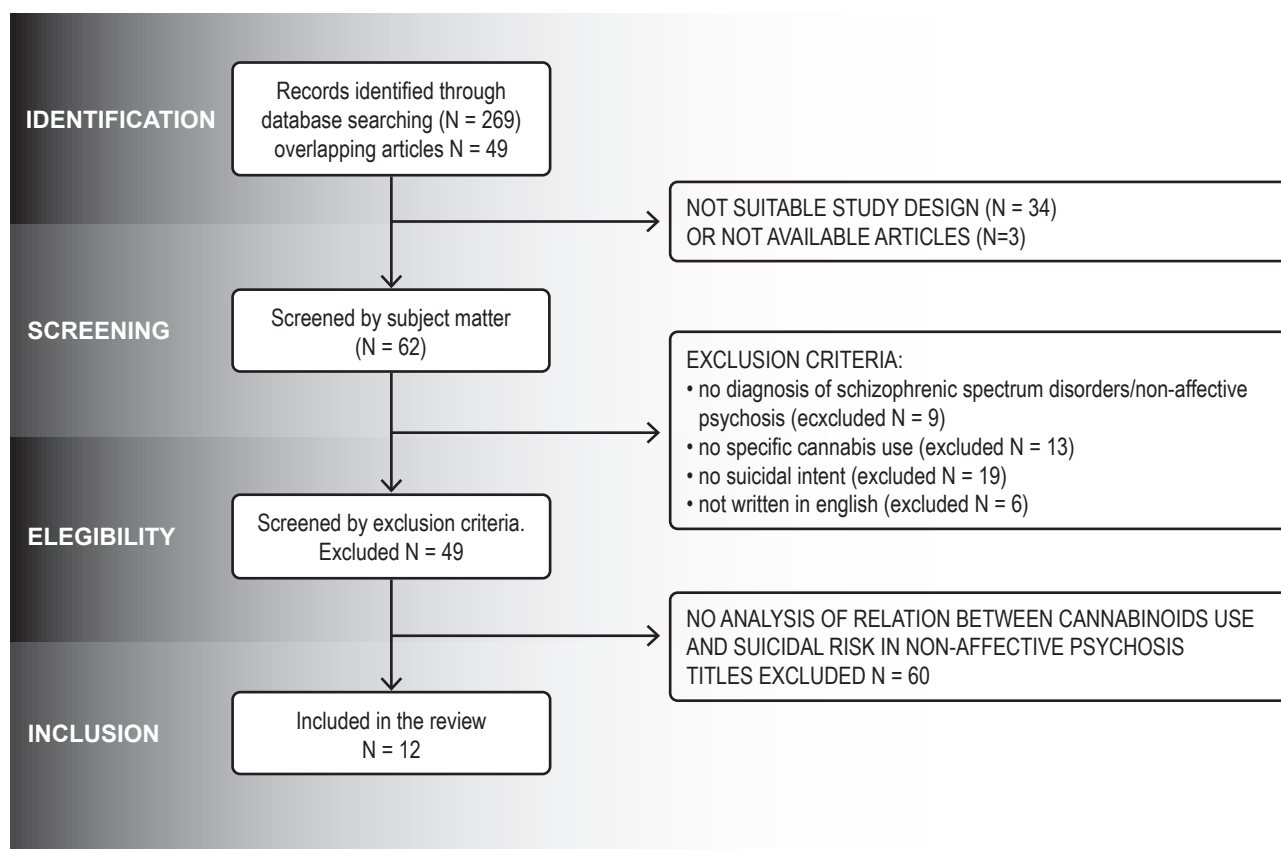
Study characteristics and main findings

Study designs of the included articles distributed as follows: 6 cross-sectional studies, 3 cohort studies, 1 case-control studies, 1 randomised double-blind study, 1 case report. (see tables "1", "2", "3").

A major cross-sectional study (Waterreus et al. 2018), involved five different centers in Australia covering a population of about 1.5 million people in total. In selected patients, although preliminary analyses showed a positive correlation between cannabis and suicide in both genders, when adjusted for risk and confounding factors (age, depression, anxiety, hallucinations, delusions, other illicit drug use, loneliness, being the victim of assault and stigma/discrimination, child-hood abuse, childhood loss and being a caregiver of their children, negative symptoms, hazardous alcohol use and homelessness) no correlation was shown. However, further examination with other covariates (gender and age) revealed that although the link between cannabis abuse and suicide ideation in psychotic disorders is absent in females, it is found when analyzing males. Adult male patients (>35 years) show an increased risk of suicide in daily users compared to non-users; unexpectedly, in young male people (18-35 years) likelihood of suicide seems to decrease as cannabis use increases.

A correlation between cannabis abuse and suicide attempts was denied in a cross-sectional study conducted by McLean (McLean et al. 2012). Multivariate models involving "cannabis use" variable was created and revealed no influence on the frequency of suicide attempts in these patients, also evaluating age and gender covariates.

The results of the previous articles seem to agree with the multicenter study conducted by Baudin (Baudin et al. 2016). Of the selected sample only 27 % (99 patients) were using cannabis or had a history of cannabis use, according to the declarations on their past habits. The study found no correlation between cannabis use and suicidal behaviour.

An opposite conclusion was achieved in the Hungarian study carried out by Makkos (Makkos et al. 2011). The study compared patients (at first hospitalization and under 35 years of age) who had been using cannabis daily (0.5-1 g/day) for at least one year to patients who had never used this drug. Patients from substance-using group were mostly males and significantly younger in age. Results showed a five-fold higher rate of suicide attempts in non-users compared to daily-users, suggesting a negative correlation between the consumption of this drug and a greater suicide risk.

Lähteenvuo (Lähteenvuo et al. 2021), contradicts, at least partially, the previous conclusions. The study,

carried out in a Finnish and a Swedish center, seems to find a positive correlation between cannabis and suicide. These cohorts were followed for 11 and 22 years in Sweden and Finland respectively.

An increased mortality due to self-inflicted death was found in cannabis users, but only in the Finnish population.

Two other studies supporting the positive correlation between cannabis and suicide, were conducted by Lückhoff (Lückhoff et al. 2014) and Østergaard (**Østergaard** et al. 2017). The cross-sectional (Lückhoff et al. 2014) shows how cannabis use or abuse is a significant predictor of suicide attempts in a population of hospital patients in the Xhosa community. The cohort study(**Østergaard** et al. 2017) focuses on the clinical information from psychiatric patients resident in Denmark. Patients were divided into the following categories: never user, former user and current user. Persons were considered current users from the date of first use and for a subsequent period of two years. After this period of current use, the person was considered a 'former user' of that substance until the start of a new treatment or the end of the study. In this study, a higher rate of suicide attempt is observed for the current user category.

The three-year longitudinal study published by Ayesa Arriola (Ayesa-Arriola et al. 2015) investigates suicide risk in patients enduring FEP, that were not previously pharmacologically treated for more than six weeks or, if previously treated, a total life time of adequate antipsychotic treatment of less than 6 weeks. Results show a positive correlation between cannabis use and suicide, especially for 'later attempters' (patients who attempted suicide after the second month of follow-up). This correlation was also confirmed by Marino (Marino et al. 2020) when studying patients who had been experiencing FEP for less than two years.

The only paper concerning SCs is from Altintas (Altintas et al. 2016). Patients with acute SCs intoxication were excluded. The article concludes that there is strong evidence of an increased risk of suicidal ideation and acts in relation to SCs-induced psychosis.

In support of the previous article, a case report (Oliveira et al. 2017) displays a severe suicidal attempt after smoking "Shiva Ultrastrong" by a patient diagnosed with paranoid schizophrenia with no history of suicide ideation or attempts.

Boggs' work focuses on CBD (Boggs et al. 2018a) , investigating the effects of oral CBD (600 mg/day) added to a stable dose of antipsychotic medication in patients with the purpose of addressing the cognitive impairments associated with schizophrenia. The exclusion criteria consisted of consumption of other substances in the last

three months and the presence of use disorder in the last six months. Results did not reveal any sign of increased suicide risk.

Most of these studies do not indicate the timeframe between cannabis use and the development of psychosis.

The studies selected in this review, with the exception of two papers, include patients with Schizophrenia spectrum disorder using the presence of a diagnosis made according to DSM-IV/V or ICD10. These manuals state as a diagnostic criterion: 'the disorder is not attributable to the physiological effects of a substance'. Thus, they are patients diagnosed with non-substance-induced schizophrenia who have substance use as a comorbidity.

The majority of these studies employed a single scale to assess symptoms of depression.

DISCUSSION

Selected cohort studies seem to agree in identifying an increased suicide risk in patients with schizophrenia spectrum disorders when exposed to cannabis use. Overall, the qualitative analysis performed classifies these three cohort studies as being of "good quality". Osteergard's (Østergaard et al. 2017) and Lähteenvuo's (Lähteenvuo et al. 2021) studies have as important strengths the large sample selected, ensuring a strong reliability in the selection; furthermore the Danish study (Østergaard et al. 2017) having maintained a follow-up of 42 years ensures a high quality of outcome measurement. However the Ayesa-Arriola (Ayesa-Arriola et al. 2015) study shows a weakness in the methodology of collecting data on cannabis exposure, which was carried out through self-reported information, thus showing a shortcoming in sample selection. It should be noted that the Lähteenvuo (Lähteenvuo et al. 2021) study, carried out in two separate cohorts, found an increased risk to such exposure in only one of the two cohorts, the Finnish one. This result, as emphasized by the authors themselves, may be explained by the important difference in the duration of follow-up in the two courts (10 years less in the Swedish court).

The only case control selected (Makkos et al. 2011) denies a correlation between cannabis use and increased suicide risk. This study from a qualitative and methodological point of view shows shortcomings both in the representativeness of the cases and in the assessment of exposure. In detail: choosing patients > 35 years old as an exclusion criterion, there is a limit to the representativeness of the cases; the methodology of ascertaining exposure is questionable in that only patients who self-report a daily consumption of 0.5-1 g of cannabis for one year are considered, thus excluding all those patients who use the

substance with different frequency and dosages or who have used it in the past.

Cross-sectional studies, due to their intrinsic methodological nature, provide with prevalence data at a specific time and thus prove the presence of a phenomenon at a specific time. Therefore, the information provided by these forms of study has a relative weight in meeting the objectives of our study.

The cross sectionals selected provide us with contradictory information. Nonetheless, a more in-depth analysis allows us to argue that these studies also suggest an increased suicidal risk in response to cannabis exposure. One of the main reasons for this is the great heterogeneity of the study populations and research instruments used. For example, the studies that do not find an increased risk of suicide (McLean et al. 2012, Baudin et al. 2016) select a different sample from the other articles: Baudin has a sample of patients selected by referral from specialists and family doctors, whereas McLean uses a sample of patients selected for genetic studies and which is represented by many relatives and twins. On the other hand, studies that find an increased suicide risk(Lückhoff et al. 2014, Marino et al, 2020. Waterreus et al. 2018) use data extrapolated from patients who have been treated in hospitals and are numerically larger and thus more representative of our study population. The case of the Waterreus study is interesting since it found an increase in suicide risk only in patients > 35 years and a decrease in risk < 35 years; this result can be explained by considering the longer drug exposition of older cannabis-abusers in comparison to younger patients, who are likely to have the same rates of suicide attempts during their future life. It should be noted, however, that the qualitative analysis of these studies classifies these studies as being of good quality, but not free of certain limitations, especially concerning the way in which data on cannabis use were collected.

In conclusion, while an initial collection of data in the literature seems to provide confounding and contradictory results, a qualitative analysis allows us to state that there appears to be a positive correlation between cannabis use and increased suicidal risk in patients on the schizophrenia spectrum.

However, we cannot identify which mode of intake (duration of intake, quantity, type) is most related to the risk of psychosis. It is also unclear whether there is a time window during which the psychotic patient appears to be at greater suicidal risk in relation to cannabis use. Certainly FEP is a time of increased vulnerability in this regard. Studies support that both lifetime and episodic cannabis use are associated with an increased risk of suicidal ideation and behavior (Karila et al. 2014; Price et al. 2009), particularly if consumed at a young age (14-15 years

old) (Gobbi et al. 2019) or in patients with preexisting nonsuicidal self-harm (Mars et al. 2019). Another study, on the other hand, claims that there is no evidence that acute use can increase suicide risk; rather, the evidence seems to support the hypothesis that chronic cannabis use may be associated with increased suicide risk (Borges et al. 2016). Furthermore, it would appear that stopping use in late adolescence does not protect against the dangerous adverse effects of cannabis(Brook et al. 2011; Epstein et al. 2015).

Another study shows how an alteration of the endocannabinoid system can predispose to suicidal behavior and wonders if cannabis, acting on this system, could be one of the causes of this dysregulation.(Mannekote Thippaiah et al. 2021)

Lastly, we have decided to discuss the most salient results broken down by the most important variables.

Gender

Focusing on the correlations with gender, most papers that display a higher likelihood of suicide attempts in psychotic subject who used cannabinoids consisted of samples where males were prevalent, and in some cases even represented the only gender evaluated. This is also the case of A. Waterreus (Waterreus et al. 2018) study whose sample is made for the 59,5 % of males. In these subjects a correlation between cannabis consumption and a greater risk for self-inflicted death is confirmed, while it is denied in females. A specific link with male gender is also seen in patients enduring firs-episode psychosis, as seen in Ayesa Arriola (Ayesa-Arriola et al. 2015) work, where male percentage in suicide attempters raised to the value of 70%. However, in this study there was no specific analysis about the interaction between the influence of cannabis on suicidal risk in this population and gender. This information however should be examined taking in consideration the already known higher rate of suicide deaths in male schizophrenic population(Sicotte et al. 2021). Epidemiological data show a male dominance also in cannabis use(Greaves & Hemsing 2020) that appears to be maintained in the male schizophrenia patients. The selected studies reflect this clear predominance of men, who appear to have higher rates of cannabis use and consequently suffer from the associated adverse effects. However, it is unclear whether the male prevalence is due to incorrect selection methods or whether fewer women actually consume cannabis. In the latter case, it would be interesting to understand what protective factors (in the case of females) or risk factors (in the case of males) lead to this difference in consumption. It would be useful to understand whether the neurobiological mechanisms

associated with an increased risk of cannabis use found in schizophrenia patients(Galletly et al. 2016) are the same in both genders, or whether the female gender implies different neurobiological mechanisms.

Age

It is difficult to draw a conclusion regarding the age variable in light of the heterogeneity of the results that emerged as well as the non-representativeness of the samples of the studies, which all differ in age distribution. The correlation noted between cannabis consumption and increased rates of suicide attempts in schizophrenic spectrum disorders in the work by Markku Lähteenvuo (Lähteenvuo et al. 2021) was only proven in one of the cohorts involved in the study, which however hosted the most numerous and youngest sample. In Lückhoff paper (Lückhoff et al. 2014), the highest peak of age distribution of first suicide attempts is shown to range from 20 to 30 years old, usually happening within 3 years of the beginning of the illness or even before when onset occurs at a later age, thus confirming that it is necessary to address young patients as the most vulnerable schizophrenic population for suicide risk in relation to cannabinoid consumption. Studies also provided contradictory findings regarding age (Bornheimer et al. 2021, Miller et al. 2019, Waterreus et al. 2018), whose study only confirmed a positive correlation between cannabis use and suicide risk in older males. Surprisingly, younger male subjects of the sample saw their risk odd decreasing while increasing cannabis use. This result can be explained considering the longer drug exposition of older cannabis-abusers in comparison to younger patients, who are likely to have the same rates of suicide attempts during their future life. Zoltan Makkos (Makkos et al. 2011) in their article found a negative correlation between cannabis use and the rates of suicides in young schizophrenic patients, being their sample made of subject under 35 years old.

FEP

The most definitive findings regarding the cannabis-suicide association emerge in patients with FEP. Both Rosa Ayesa-Arriola (Ayesa-Arriola et al. 2015) and Leslie Marino (Marino et al. 2020) works found a positive correlation between cannabis consumption and increased suicide attempts and deaths during FEP. In the former paper(Ayesa-Arriola et al. 2015) cannabis use, as well as depressive symptoms and a shorter duration of untreated psychosis (DUP), is identified as a specific risk factor in "late attempters", patients who attempted suicide beyond

the two months since FEP. "Late attempts" seem to differ in terms of risk factors compared to early attempts, which appear to be the direct consequence of the acute state of psychosis. It is noteworthy that authors not only worried about immediate risk after cannabis consumption, but also showed preoccupation that drug use could represent a long-term threat for life. In the Marino paper (Marino et al. 2020) it is specifically persistent use to be suggested as a risk factor for self-inflicted death in patients enduring FEP. Nevertheless, there are not enough information or objective measures about the frequency and the duration of cannabinoid abuse to utterly assess how these variables modify the entity of suicidal risk.

SCs and CBD

Specific consumption of Synthetic Cannabinoids was examined in the article written by Altintas (Altintas et al. 2016) and in case report described by Oliveira (Oliveira et al. 2017). SCs use has not only been related to suicide risk in already diagnosed schizophrenic spectrum disorders, but SC-induced psychosis also seems to be characterized by an extremely high rate of suicide ideation and attempts. No female patients were included in these studies. Moreover, in Altintas (Altintas et al. 2016) depression in non-affective psychosis is found to be related, as already mentioned, both to suicidality in psychotic disorders and synthetic cannabinoids use.

The results regarding clinical consequences of cannabidiol consumption, presented in a case-control study (Boggs et al. 2018a, 2018b) concluded that no suicide risk was reported in literature in association with CBD treatment in schizophrenic patients. Nevertheless, they seemed to confirm the neuroprotective and precognitive effect already found in literature.

AFFECTIVE EPISODES

Co-occurence of depressive episodes is central to suicide risk in schizophrenic patients, especially during FEP (Berardelli et al. 2021).

Depressive symptomatology is present in 30% of cases during the first psychotic episode and reaches 70% when considered over the entire duration of the pathology (Maj et al. 2021, Peralta and Cuesta, 2009). Often it is difficult to distinguish between affective episodes and primary psychosis. The finding of sadness or feelings of guilt often suggests the presence of depressive symptomatology (Maj et al. 2021); The Calgary Depression Scale for Schizophrenia is the best option for assessing depression in the context of psychotic symptoms (Addington et al. 1992). Depressive symptomatology is also associated

with an increased risk of suicide (Hor and Taylor, 2010). Remarkably, according to the scientific literature, some suicide risk factors in schizophrenic patients, such as depression (Bornheimer et al. 2021, Crebbin et al. 2008, Fenton WS 2000, Gobbi et al. 2019, Vinod and Hungund, 2006) may be influenced by cannabis use. Indeed, chronic cannabis use has been shown to correlate with dysregulation of the cannabinoid system(Ceccarini et al. 2015, Hirvonen et al. 2012). Such dysregulation may be associated with depression and suicide risk (Boorman et al. 2016, Vinod and Hungund, 2006, Volkow et al. 2017).

Many of the studies selected in our review look for depressive symptoms or EDM in the samples examined and correct the final data by considering depression as a confounding factor.

Some studies (Ayesa-Aryola et al. 2015, Waterreus et al. 2016, Altintas et al. 2016, Baudin et al. 2016, Marino et al. 2016) are more accurate in searching for depressive symptoms as they use accurate diagnostic instruments (psychometric scales).

The studies by Ayesa-Aryola and Waterreus, when correcting the results by considering depression as a confounding factor, detect a weaker association between cannabis use and suicide risk.

The Altintas study (2016) also detects depressive symptoms and corrects the results for this variable, finding higher suicide rates both in synthetic cannabinoid-induced psychosis and in patients with Schizophrenia who use this substance.

Marino's (Marino et al. 2020) study searches for the presence of depressive symptoms using the MIRECC Global Assessment of Functioning (GAF), but does not correct the results for this variable.

Baudin (Baudin et al. 2016) in his study searches for depressive symptoms and corrects the data for this variable, finding clinical and functional worsening associated with cannabis use but no increased suicidal risk.ù

Østergaard and colleagues (**Østergaard** et al. 2017) found that patient with depression, but non schizophrenic, had the lowest prevalence of lifetime SUDs, suicides and suicide attempts and cannabis consupmtpion and hard drug use disorders were most widespread in the population with schizophrenia, followed by personality disorder, bipolar disorder, and depression.

A previous study (Flanagan and Compton, 2012) found that depression, insight and suicidality were predictors of suicidal ideation prior to the initial hospitalization. Hence, depression seems to be a high risk factor for suicide in both early and later stages of FEP; finally depression in the prodromal stage was reported to predict suicidality at first

presentation and further depressive episodes both in the acute and recovery stages of FEP which appears to challenge the so-called demoralization syndrome (Drake and Cotton, 1986, Upthegrove et al. 2014, Pompili et al. 2011)

In conclusion, we cannot rule out the possibility that the presence or absence of depressive symptomatology may be a confounding factor in the final outcome of our review. It remains to be clarified whether cannabis may be the cause of the onset of depressive symptomatology and thus increased suicide risk or whether cannabis and depression are but two independent factors and both may cause increased risk.

Limitations

Limitations regarding papers included are primarily represented by the different evaluation scales and measures used to identify and study the variables involved in our hypothesis, such as diagnosis, cannabis consume and suicide ideation/attempt. In fact, non-affective psychosis and schizophrenia spectrum disorders were not diagnosed according to a single manual parameter but following criteria from DMS- IV, DSM- V, ICD 10. Also cannabis use is assessed trough all kinds of methods such as self-reported information, or collecting diagnosed SUD recorded in treatment register. Suicidal risk makes no exception, since it is was analyzed by the means of scales, such as National Survey of Mental Health and Wellbeing or Columbia-Suicide Severity Rating Scale, register-based data and medical reports. This heterogeneity makes results difficult to compare and question the reliability of the conclusions presented. Moreover, cannabis use is calculated only on the basis of frequency of assumption, ignoring the amount and type of cannabis consumed. Cannabis contains hundreds of different molecules with different actions. There are also many varieties of cannabis that contain psychoactive substances greatly differing in type, quantity and ratio (Cohen et al. 2018). In addition, cannabis bought illegally on the black market may often have been contaminated with other substances not naturally found in the plant (McLaren et al. 2008). Cannabis has multiple modes of intake (combustion, vaporization and ingestion) and consequently may release different metabolites, in different concentrations (Grotenhermen 2003). Furthermore, it is important to highlight that most samples studied cannot be considered representative of the general population suffering from schizophrenia spectrum disorder. Lastly, few studies were able to robustly control for the presence of confounding factors, particularly polysubstance use.

CONCLUSIONS

Emerging data on the correlation between cannabis use and suicide risk in patients with schizophrenic spectrum disorders are not sufficient to draw firm conclusions. Nonetheless these studies seem to point toward a positive correlation of cannabis use with increased suicide risk, particularly regarding FEP and male gender.

In directing future research, it would be important to: homogenize data collection instruments, specifically investigate the type and amount of cannabis used, enroll samples which are representative of the population, study the relationship between cannabis and the other suicide risk factors. In fact, it is necessary to clarify not only the direct relationship between cannabis and suicide risk, but also the correlation between cannabis use and independent risk factors for suicide risk, in particular depressive symptoms.

Moreover, the results indicate a different gender and age-related susceptibility in response to cannabinoids regarding suicide risk, hence laying the foundations for future inquests to understand whether regular cannabis use has an influence on specific biological mechanisms that could explain the differences observed. In conclusion, clinicians should be aware of the possibility of a higher risk of suicidal behavior associated specifically with cannabis use for men and patients during FEP.

References

1. Addington D, Addington J, Maticka-Tyndale E, Joyce J. Reliability and validity of a depression rating scale for schizophrenics. Schizophr Res 1992; 6, 201–208.
2. Altintas M, Inanc L, Oruc G, Arpacioglu S, Gulec H: Clinical characteristics of synthetic cannabinoid-induced psychosis in relation to schizophrenia: A single-center cross-sectional analysis of concurrently hospitalized patients. Neuropsychiatr Dis Treat 2016; 12, 1893–1900.
3. Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE: Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ 2002; Nov 23;325(7374):1212-3.
4. Ayesa-Arriola R, Alcaraz EG, Hernández BV, Pérez-Iglesias R, López Moríñigo JD, Duta R et al.: Suicidal behaviour in first-episode non-affective psychosis: Specific risk periods and stage-related factors. Eur Neuropsychopharmacol 2015; 25, 2278–2288.
5. Barbeito S, Vega P, Sánchez-Gutiérrez T, Becerra JA, González-Pinto A, Calvo A: A systematic review of suicide and suicide attempts in adolescents with psychotic disorders. Schizophr Res 2021; 235, 80–90.
6. Baudin G, Godin O, Lajnef M, Aouizerate B, Berna F, Brunel L. et al.: Differential effects of childhood trauma and cannabis use disorders in patients suffering from schizophrenia. Schizophr Res 2016: 175, 161–167.
7. Berardelli I, Rogante E, Sarubbi S, Erbuto D, Lester D, Pompili M. The Importance of Suicide Risk Formulation in Schizophrenia. Front Psychiatry 2021: 12.
8. Boggs Douglas L, Nguyen JD, Morgenson D, Taffe MA, Ranganathan M: Clinical and Preclinical Evidence for Functional Interactions of Cannabidiol and Δ9-Tetrahydrocannabinol. Neuropsychopharmacology 2018a; 43, 142–154.
9. Boggs Douglas L, Surti T, Gupta A, Gupta S, Niciu M, Pittman B et al.: The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial. Psychopharmacology (Berl) 2018b; 235, 1923–1932.
10. Boorman E, Zajkowska Z, Ahmed R, Pariante CM, Zunszain PA. Crosstalk between endocannabinoid and immune systems: A potential dysregulation in depression? Psychopharmacology (Berl) 2016; May;233(9):1591-604.
11. Borges G, Bagge CL, Orozco R. A literature review and meta-analyses of cannabis use and suicidality. J Affect Disord 2016; 195, 63–74.
12. Bornheimer LA, Wojtalik JA, Li J, Cobia D, Smith MJ: Suicidal ideation in first-episode psychosis: Considerations for depression, positive symptoms, clinical insight, and cognition. Schizophr Res 2021; 228, 298–304.
13. Breitborde NK, Wastler H, Pine JG, Moe AM: Suicidality and social problem-solving skills among individuals with first-episode psychosis participating in Coordinated Specialty Care. Early Interv Psychiatry 2021a; 15, 497–504.

14. Breitborde NJK., Wastler H, Pine JG, Moe AM: Suicidality and social problem-solving skills among individuals with first-episode psychosis participating in Coordinated Specialty Care. Early Interv Psychiatry 2021b; 15, 497–504.

15. Brook JS, Lee JY, Brown EN, Finch SJ, Brook DW. Developmental Trajectories of Marijuana Use from Adolescence to Adulthood: Personality and Social Role Outcomes. Psychol Rep 2011; 108, 339–357.

16. Canal-Rivero M, López-Moríñigo JD, Setién-Suero E, Ruiz-Veguilla M, Ayuso-Mateos JL, Ayesa-Arriola R, Crespo-Facorro B:Predicting suicidal behaviour after first episode of non-affective psychosis: The role of neurocognitive functioning. Eur Psychiatry 2018; 53, 52–57.

17. Castelein S, Liemburg EJ, de Lange JS, van Es FD, Visser E, Aleman A et al.: Suicide in Recent Onset Psychosis Revisited: Significant Reduction of Suicide Rate over the Last Two Decades — A Replication Study of a Dutch Incidence Cohort. PLoS One 2015; 10, e0129263.

18. Ceccarini J, Kuepper R, Kemels D, van Os J, Henquet C, van Laere K. [18F]MK-9470 PET measurement of cannabinoid CB1 receptor availability in chronic cannabis users. Addiction Biology 2015; 20, 357–367.

19. Cohen K & Weinstein AM: Synthetic and Non-synthetic Cannabinoid Drugs and Their Adverse Effects-A Review From Public Health Prospective. Front Public Health 2018; 6.

20. Cohen K, Weizman A, Weinstein A: Positive and Negative Effects of Cannabis and Cannabinoids on Health. Clin Pharmacol Ther 2019; 105, 1139–1147.

21. Crebbin K, Mitford E, Paxton R, Turkington D. First-episode psychosis: An epidemiological survey comparing psychotic depression with schizophrenia. J Affect Disord 2008; 105, 117–124.

22. Deep CA, Villa J, Schembari BC, Harvey PD, Pinkham A: Social cognition and short-term prediction of suicidal ideation in schizophrenia. Psychiatry Res 2018; 270:13-19.

23. Di Forti M, Morgan C, Dazzan P, Pariante C, Mondelli V, Marques TR et al. High-potency cannabis and the risk of psychosis. Br J Psychiatry 2009; 195(6):488–91.

24. Di Forti M, Marconi A, Carra E, Fraietta S, Trotta A, Bonomo M et al: Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: A case-control study. Lancet Psychiatry 2015; Mar 1;2(3):233–8.

25. Drake RE & Cotton PG. Depression, hopelessness and suicide in chronic schizophrenia. Br. J. Psychiatry 1986; 148, 554–559.

26. Epstein M, Hill KG, Nevell AM, Guttmannova K, Bailey JA, Abbott RD, Kosterman R, Hawkins JD. Trajectories of marijuana use from adolescence into adulthood: Environmental and individual correlates. Dev Psychol 2015; 51, 1650–1663.

27. Fantegrossi WE, Moran JH, Radominska-Pandya A, Prather PL: Distinct pharmacology and metabolism of K2 synthetic cannabinoids compared to Δ9-THC: Mechanism underlying greater toxicity? Life Sci 2014; 97, 45–54.

28. Fattore L: Synthetic Cannabinoids—Further Evidence Supporting the Relationship Between Cannabinoids and Psychosis. Biol Psychiatry 2016; 79, 539–548.

29. Fenton WS: Depression, suicide, and suicide prevention in schizophrenia. Suicide Life Threat Behav 2000; Spring 30, 34–49.

30. Flanagan P & Compton MT. A comparison of correlates of suicidal ideation prior to initial hospitalization for first-episode psychosis with prior research on correlates of suicide attempts prior to initial treatment seeking. Early Interv. Psychiatry 2012; 6, 138–144.

31. Galletly C, Castle D, Dark F, Humberstone V, Jablensky A, Killackey E et al.:Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. Aust N Z J Psychiatry 2016; May;50(5):410-72.

32. Gobbi G, Atkin T, Zytynski T, Wang S, Askari S, Boruff J et al.: Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood: A Systematic Review and Meta-analysis. JAMA Psychiatry 2019; 76, 426. vinod

33. Greaves L & Hemsing N: Sex and gender interactions on the use and impact of recreational cannabis. Int J Environ Res Public Health 2020; Jan 14;17(2):509. DOI:10.3390/ijerph17020509

34. Grotenhermen F: Pharmacokinetics and Pharmacodynamics of Cannabinoids. Clin Pharmacokinet 2003; 42(4):327-60.

35. Hirvonen J, Goodwin RS, Li CT, Terry GE, Zoghbi SS, Morse C et al.: Reversible and regionally selective down-regulation of brain cannabinoid CB 1 receptors in chronic daily cannabis smokers. Mol Psychiatry 2012; 17, 642–649.

36. Hor K & Taylor. Review: Suicide and schizophrenia: a systematic review of rates and risk factors. Journal of Psychopharmacology 2010; 24, 81–90.

37. Iseger TA & Bossong MG: A systematic review of the antipsychotic properties of cannabidiol in humans. Schizophr Res 2015; 162, 153–161.

38. Karila L, Roux P, Rolland B, Benyamina A, Reynaud M, Aubin HJ, Lançon C. Send Orders for Reprints to reprints@benthamscience.net Acute and Long-Term Effects of Cannabis Use: A Review, Current Pharmaceutical Design 2014; 20(25):4112-8.

39. Kay SR; Fiszbein A; Opler LA. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. Schizophr Bull 1987; 13, 261–276.

40. Lähteenvuo M, Batalla A, Luykx JJ, Mittendorfer-Rutz E, Tanskanen A, Tiihonen J et al.: Morbidity and mortality in schizophrenia with comorbid substance use disorders. Acta Psychiatr Scand 2021; 144, 42–49.

41. Large M, Sharma S, Compton MT, Slade T, Nielssen O: Cannabis use and earlier onset of psychosis: A systematic meta-analysis. Arch Gen Psychiatry 2011; Jun;68(6):555–61.

42. Lückhoff M, Koen L, Jordaan E, Niehaus D: Attempted suicide in a Xhosa schizophrenia and schizoaffective disorder population. Suicide Life Threat Behav 2014; 44, 167–174.

43. Makkos Z, Fejes L, Inczédy-Farkas G, Kassai-Farkas A, Faludi G, Lazary J: Psychopharmacological comparison of schizophrenia spectrum disorder with and without cannabis dependency. Prog Neuropsychopharmacol Biol Psychiatry 2011;35, 212–217.

44. Mars B, Heron J, Klonsky ED, Moran P, O'Connor RC, Tilling K, Wilkinson P, Gunnell D. Predictors of future suicide attempt among adolescents with suicidal thoughts or non-suicidal self-harm: a population-based birth cohort study. Lancet Psychiatry 2019; 6, 327–337.

45. Mannekote Thippaiah S, Iyengar SS, Vinod KY: Exo- and Endo-cannabinoids in Depressive and Suicidal Behaviors. Front Psychiatry 2021; Apr 23;12:636228.

46. Marino L, Scodes J, Richkin T, Alves-Bradford JM, Nossel I, Wall M, et al.: Persistent cannabis use among young adults

with early psychosis receiving coordinated specialty care in the United States. Schizophr Res 2020; 222, 274–282.

47. Maj M, Os J, de Hert M, Gaebel W, Galderisi S, Green MF, Guloksuz S, Harvey PD, Jones PB, Malaspina D, McGorry P, Miettunen J, Murray RM, Nuechterlein KH, Peralta V, Thornicroft G, Winkel R, Ventura J.The clinical characterization of the patient with primary psychosis aimed at personalization of management. World Psychiatry 2021; 20, 4–33.

48. McGinty J, Sayeed Haque M, Upthegrove R: Depression during first episode psychosis and subsequent suicide risk: A systematic review and meta-analysis of longitudinal studies. Schizophr Res 2018; 195, 58–66.

49. McLaren J, Swift W, Dillon P, Allsop S: Cannabis potency and contamination: A review of the literature. Addiction 2008; Jul;103(7):1100-9.

50. Miller BJ, Parker CB, Rapaport MH, Buckley PF, McCall W: Insomnia and suicidal ideation in nonaffective psychosis. Sleep 2019; 42. DOI:10.1093/sleep/zsy215

51. Oliveira PM dos S, Morais ASF, Madeira NGGF: Synthetic Cannabis Analogues and Suicidal Behavior: Case Report. J Addict Med 2017; 11, 408–410.

52. Østergaard MLD, Nordentoft M, Hjorthøj C: Associations between substance use disorders and suicide or suicide attempts in people with mental illness: a Danish nation-wide, prospective, register-based study of patients diagnosed with schizophrenia, bipolar disorder, unipolar depression or personality disorder. Addiction 2017; 112, 1250–1259.

53. Papanti D, Schifano F, Botteon G, Bertossi F, Mannix J, Vidoni D et al. "Spiceophrenia": A systematic overview of "spice"- related psychopathological issues and a case report. Hum Psychopharmacol 2013; Jul;28(4):379–89.

54. Patel SJ, Khan S, M S, Hamid P: The Association Between Cannabis Use and Schizophrenia: Causative or Curative? A Systematic Review. Cureus 2020; Jul 21. DOI:10.7759/cureus.9309

55. Pelizza L, Pompili M, Azzali S, Paterlini F, Garlassi S, Scazza I et al.: Suicidal thinking and behaviours in First Episode Psychosis: Findings from a 3-year longitudinal study. Early Interv Psychiatry 2021; 15, 624–633.

56. Peralta V & Cuesta M. Characterization of affective domains within the nonaffective psychotic disorders. Schizophr Res 2009; 111, 61–69.

57. Pompili M, Serafini G, Innamorati M, Lester D, Shrivastava A. Girardi P, Nordentoft M. Suicideriskin first episode psychosis: a selective review of the current literature. Schizophr Res 2011; 129,1–11.

58. Price C, Hemmingsson T, Lewis G, Zammit S, Allebeck P. Cannabis and suicide: longitudinal study. British Journal of Psychiatry 2009; 195, 492–497.

59. Ricci V, Martinotti G, Ceci F, Chiappini S, di Carlo F, Burkauskas J et al.: Duration of Untreated Disorder and Cannabis Use: An Observational Study on a Cohort of Young Italian Patients Experiencing Psychotic Experiences and Dissociative Symptoms. Int J Environ Res Public Health 2021; Nov 30;18(23):12632. DOI:10.3390/ijerph182312632

60. Sicotte R, Iyer SN, Kiepura B, Abdel-Baki A: A systematic review of longitudinal studies of suicidal thoughts and behaviors in first-episode psychosis: course and associated factors. Soc Psychiatry Psychiatr Epidemiol 2021; 56, 2117–2154.

61. Upthegrove R, Ross K, Brunet K, McCollum R, Jones L. Depression in first episodepsychosis:theroleofsubordination and shame.PsychiatryRes 2014; 217,177–184.

62. Vinod KY, Hungund BL. Role of the endocannabinoid system in depression and suicide. Trends Pharmacol Sci 2006; Oct;27(10):539-45.

63. Volkow ND, Hampson AJ, Baler RD. Don't Worry, Be Happy: Endocannabinoids and Cannabis at the Intersection of Stress and Reward. Annu Rev Pharmacol Toxicol 2017; Jan 6;57:285-308.

64. Waterreus A, di Prinzio P, Badcock JC, Martin-Iverson M, Jablensky A, Morgan VA: Is cannabis a risk factor for suicide attempts in men and women with psychotic illness? Psychopharmacology (Berl) 2016; 235, 2275–2285.

65. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al.: The Newcastle-Ottawa Scale NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/ clinical_epidemiology/oxford.asp. 2013.

66. Yin Y, Tong J, Huang J, Tian B, Chen S, Cui Y et al.: Suicidal ideation, suicide attempts, and neurocognitive dysfunctions among patients with first-episode schizophrenia. Suicide Life Threat Behav 2020; 50, 1181–1188.

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