



Relationship between cannabis and psychosis: Reasons for use and associated clinical variables



Anna Mané^{a,b,*}, Miguel Fernández-Expósito^c, Daniel Bergé^{a,b}, Laura Gómez-Pérez^a,
Agnés Sabaté^a, Alba Toll^a, Laura Diaz^a, Cristobal Diez-Aja^a, Víctor Perez^{a,b}

^a IMIM (Hospital del Mar Medical Research Institute) – Neurosciences, Psychiatry, Barcelona, Spain

^b Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Spain

^c Universitat Pompeu Fabra and Universitat Autònoma Barcelona, Barcelona, Spain

ARTICLE INFO

Article history:

Received 25 October 2014

Received in revised form

16 July 2015

Accepted 26 July 2015

Available online 28 July 2015

Keywords:

Cannabis

First-episode

Reasons for use

Schizophrenia

Self-medication

ABSTRACT

The mechanism underneath the relationship between cannabis and psychosis remains controversial, for which several hypotheses have been proposed, including cannabis as self-medication and cannabis as a risk for the development of psychosis. The aim of this work was to study the relationship between cannabis and psychosis in first-episode psychosis cannabis users and non-users, and non-psychotic cannabis users. The age at the first psychotic episode, duration of untreated psychosis, psychopathology and reasons for cannabis use were assessed. First-episode psychosis cannabis users showed an earlier age at psychosis onset than non-user patients. No significant differences in symptomatology were found. The distinguishing reasons to use cannabis for patients with first-episode psychosis with respect to non-psychotic users were to arrange their thoughts and deal with hallucinations and suspiciousness. These findings are in agreement with both hypotheses: self-medication and secondary psychosis hypothesis. However, longitudinal prospective cohort studies assessing reasons for cannabis use are needed to investigate both hypotheses and their complementarity.

© 2015 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Patients with psychosis have a higher prevalence of substance use, particularly cannabis use. In a meta-analysis, patients with psychosis presented a median lifetime cannabis use disorder rate of 27.1% (Koskinen et al., 2010), whereas in the general population lifetime rates are usually around 10% (Haberstick et al., 2014).

Importantly, in patients with psychosis, cannabis use has been related with poor adherence, more relapses and persistent positive symptoms (Grech et al., 2005; Linszen et al., 1994; Schimmelmann et al., 2012).

Various authors have tried to understand the relationship between substance use, including cannabis use, and psychosis. Several hypotheses have been developed for substance use in general, but they also apply to cannabis use. The two most studied are:

The hypothesis that proposes that psychosis is secondary to substance use, meaning that substance use increases the risk of developing psychosis (Semple et al., 2005). In the case of cannabis, this hypothesis is supported by numerous studies, including a

meta-analysis conducted on 35 longitudinal population studies, showing that patients with a history of cannabis use have an increased risk of developing psychosis (Andreasson et al., 1989; Moore et al., 2007). Furthermore, various studies have shown that patients with cannabis use have an earlier age of psychosis onset (Di Forti et al., 2014; Large et al., 2011). However, in this regard, some authors have proposed that an earlier age of psychosis onset in cannabis users is just secondary to a shorter Duration of Untreated Psychosis (DUP), as their symptoms may become more obvious more quickly (Compton et al., 2009). Nevertheless, there is no consensus on this matter, as some authors have found longer DUP in those first episode patients who had used cannabis, suggesting longer treatment delays in cannabis users (Broussard et al., 2013).

The hypothesis that proposes that substance use is secondary to the psychotic illness (Self-medication hypothesis), meaning that patients use cannabis (or other substances) to relieve particular symptoms (positive, negative) caused by psychosis (Khantzian, 1985). Substances are not chosen randomly, there exists psychopharmacological specificity. Self-medication of antipsychotic side effects has also been proposed (Schneier and Siris, 1987). A variation of the self-medication hypothesis has been developed: the alleviation of dysphoria model (Khantzian, 1997). It proposes that patients with psychosis use substances to alleviate unpleasant

* Corresponding author at: Passeig Marítim Barceloneta 25–29, Barcelona 08003, Spain. Fax: +34 93 2483445.

E-mail address: manesantacana@yahoo.es (A. Mané).

Table 1

Overview of previous studies assessing reasons of substance use (including cannabis use) in psychotic patients.

Authors	Diagnosis	Cannabis use criteria	Reason of use assessment
Dixon et al. (1991)	Schizophrenia, Schizoaffective Disorder, Schizophreniform Disorder	CUD previous 6 months	Dixon's questionnaire
Warner et al. (1994)	Schizophrenia, Schizoaffective Disorder, Bipolar Disorder	No substance use criteria	Semi-structured interview
Addington and Duchak (1997)	Schizophrenia, Schizoaffective Disorder	CUD	Adapted Dixon's questionnaire
Fowler et al. (1998)	Schizophrenia	Cannabis use	Open interview
Spencer et al. (2002)	Psychosis	Cannabis use	Adapted <i>Drinking Motives Questionnaire (DMQ)</i>
Goswami et al. (2004)	Schizophrenia	CUD previous month	Adapted Dixon's questionnaire (<i>State Reasons Scale</i>),
Green et al. (2004)	Schizophrenia, Schizoaffective Disorder	Cannabis use	Open interview
Schofield et al. (2006)	Schizophrenia, Schizoaffective Disorder, Schizophreniform Disorder	Cannabis use	Adapted Dixon's questionnaire
Schaub et al. (2008)	Schizophrenia	CUD	15-item questionnaire
Saddichha et al. (2010)	Schizophrenia Bipolar disorder	CUD	Open interview
Archie et al. (2013)	First Episode Psychosis	No substance use criteria	Open interview
Kolliakou et al. (2015)	First Episode Psychosis	Cannabis use	Reasons for Use Scale (RFUS)

CUD. Cannabis use disorder.

states associated with psychosis, such as boredom or depression. In this case, it has been suggested that patients do not choose a specific substance to relieve their discomfort.

Various authors have investigated reasons for cannabis use in patients with psychosis ([Addington and Duchak, 1997](#); [Archie et al., 2013](#); [Dixon et al., 1991](#); [Fowler et al., 1998](#); [Goswami et al., 2004](#); [Green et al., 2004](#); [Kolliakou et al., 2015](#); [Saddichha et al., 2010](#); [Schaub et al., 2008](#); [Schofield et al., 2006](#); [Spencer et al., 2002](#); [Warner et al., 1994](#)) (see [Table 1](#)). However, methodological aspects limit the ability to draw appropriate conclusions. For instance, as you can see in [Table 1](#), some studies include patients with cannabis use disorders, whereas others include just cannabis users. Moreover, most of previous studies include patients with different diagnoses (Schizophrenia, Bipolar Disorder) without specifying illness stage, and few studies have been carried out in first-episode psychosis patients ([Archie et al., 2013](#); [Kolliakou et al., 2015](#)). Patients at different illness stages have different characteristics and therefore they may have different needs ([Lewis and Lieberman, 2000](#)). Furthermore, different instruments have been used to assess reasons of use (registry on a list, open interview). However, it is important to highlight that one instrument, or an adaptation of it, has been employed in various studies: Dixon's questionnaire. On the other hand, to our knowledge, only three studies have used a control group (cannabis users without psychosis) ([Green et al., 2004](#); [Saddichha et al., 2010](#); [Schaub et al., 2008](#)). We believe the best way to test the self-medication hypothesis is to determine whether individuals with psychosis use cannabis for differential reasons than control age- and gender-matched individuals without psychosis, to distinguish if psychosis patients have specific reasons not just related to using cannabis at their age.

Previous studies that have been performed with a control group (cannabis users without psychosis) have also used heterogeneous methodology. They point to differential reasons to use cannabis in people with psychosis but further research is needed to confirm these findings.

Finally, most of previous studies have been carried out to study both hypotheses separately, without considering them complementary, as some authors have proposed ([Grech et al., 2005](#)).

The aim of the present study is to try to understand those factors influencing the relationship between cannabis and psychosis in first-episode psychosis patients, including self-medication and cannabis use as a psychosis risk factor, which may help to implement new and specific therapeutic approaches in the future. To this end, we will: 1) Examine the association between cannabis use, illness onset and psychopathology in a group of patients with

first-episode psychosis 2) Compare reasons of cannabis use between those first-episode patients who use cannabis and a control group of non-psychotic cannabis users. We hypothesize that first-episode psychosis patients who use cannabis will have an earlier age at psychosis onset (after taking into account DUP and gender), and a specific psychopathological pattern (more positive symptoms). We also hypothesize that first-episode cannabis users will have differential reasons to use cannabis than non-psychotic users.

2. Methods

2.1. First-episode psychosis characteristics

A total of 119 consecutive first-episode psychotic patients who attended the First-episode Psychosis Program at Hospital del Mar between 2008 and June 2014 were included. Inclusion criteria for patients were as follows: i) 18–35 years of age; ii) Diagnostic and Statistical Manual of Mental Disorders-fourth edition (text revision) criteria for Brief Psychotic Disorder, Schizophreniform Disorder, Schizophrenia with less than one year of symptom evolution, or Unspecified Psychosis; iii) absence of any severe neurologic medical condition or severe cranioencephalic trauma in medical history; iv) estimated intelligence quotient above 80; v) absence of any substance abuse/dependence disorder except for cannabis and nicotine.

Patients were considered cannabis users if they used cannabis at least weekly previous six months.

Clinical and sociodemographic variables, including age at psychosis onset, gender, DUP, symptomatology, cannabis use (number of joints per week, age at cannabis use onset), and psychopathology with the Positive and Negative Syndromes Scale (PANSS) ([Kay et al., 1990](#)), were studied in two groups of patients with first-episode psychosis: cannabis users and non-users.

Age at psychosis onset was defined as the first time the patient went to a psychiatrist or was admitted to a hospital and was diagnosed with a first-episode of psychosis. We decided to use this criterion as it is an objective method, used in several of previous Schizophrenia studies ([Barnes et al., 2006](#); [Di Forti et al., 2014](#)). DUP was considered the time from the first continuous psychotic symptom to the first time the patient went to a psychiatrist or was admitted to a hospital and was diagnosed with a first episode of psychosis. Data regarding DUP and age at psychosis onset was obtained from medical reports and information from patients and their relatives obtained by psychiatrists in charge of the patients, with large experience in treating Schizophrenia patients.

2.2. Reasons for cannabis use

First-episode psychosis patients who were identified as cannabis users and control age- and gender-matched non-psychotic cannabis users were asked to complete Dixon's questionnaire (Dixon et al., 1991) to assess reasons for cannabis use. It is a self-reported 15-item questionnaire with dichotomous (yes/no) responses to queries for various reasons of use. However, we left out the item relieve side-effects of medication as first-episode patients where not taking medication when they were admitted. Control subjects were recruited using advertisements in various locations, and only those who used cannabis at least weekly were accepted. Participants were evaluated using the Mini International Neuropsychiatric Interview (Amorim et al., 1998), and those who screened positive for any other psychiatric disorder were excluded from the study.

2.3. Ethics and consent

All subjects gave written informed consent in accordance with the respective clinical ethical committee. This study was carried out in agreement with the ethical standards established in the Declaration of Helsinki and local legislation with respect to confidentiality and data protection.

2.4. Statistical analysis

Statistical analysis was performed with SPSS statistical software (version 19.0; SPSS Inc., Chicago, IL, USA).

Univariate analyses were performed to assess the differences in age at psychosis onset, gender, DUP and PANSS total and subscale scores between psychotic cannabis users and non-users, as well as to assess differences in reasons for cannabis use between psychotic cannabis users and non-psychotic cannabis users (independent sample *t*-test or Chi-square when applicable).

A backwards elimination regression model was also performed, with age at psychosis onset as the dependent variable, and DUP, gender and cannabis use (yes/no) as independent variables.

$P \leq 0.05$ was considered as statistically significant.

3. Results

3.1. Psychotic cannabis users versus non-users

Demographic, clinical characteristics and their analyses are shown in Table 2.

The age of psychosis onset was significantly younger in users compared to non-users. Furthermore, cannabis users showed a

Table 2
Demographic and clinical differences between first-episode psychosis (FEP) cannabis users and non-users.

	FEP cannabis users	FEP non-users	<i>p</i> , statistic
Age (m, s.d.)	23.74 (4.11)	26.83 (5.01)	$p < 0.001$, $t = 5.03$
Gender (Males)	70%	53%	$p = 0.009$, $\chi^2 = 7.03$
DUP days (m, s.d.)	65.05 (132.29)	147.28 (235.15)	$p = 0.022$, $t = 2.54$
PANSS-Total (m, s.d.)	85.38 (17.55)	85.34 (19.65)	$P = 0.99$, $t = -0.01$
PANSS-Positive (m, s.d.)	26.98 (6.21)	25.10 (6.69)	$p = 0.11$, $t = -1.59$
PANSS-Negative	15.64 (6.79)	17.16 (6.54)	$p = 0.22$, $t = 1.24$
PANSS-General (m, s.d.)	42.77 (10.70)	43.09 (10.51)	$p = 0.87$, $t = 0.16$

m: mean; *s.d.*: standard deviation.

Table 3

Demographic characteristics of non-psychotic cannabis users and first-episode (FEP) cannabis users.

	Non-psychotic cannabis users	FEP cannabis users	<i>P</i> , statistic
Age (m, s.d.)	24.90 (3.69)	23.94 (4.12)	$P = 0.24$, $t = 1.19$
Gender (Male)	62.5%	70.8%	$P = 0.27$, $\chi^2 = 1.19$
Age at cannabis use onset (m,s.d.)	15.83 (2.53)	16.48 (2.39)	$P = 0.19$, $t = -1.31$

m: mean; *s.d.*: standard deviation.

significantly shorter DUP than non-users. Among cannabis users, there were significantly more men than women. There were no significant differences between groups in PANSS total score or subscale scores. In the multiple regression analysis, cannabis use ($B = -2.71$; $P = 0.002$) and male gender ($B = 1.73$; $P = 0.05$) were the variables that predicted earlier age at psychosis onset.

3.2. Psychotic versus non-psychotic cannabis users

Of the 58 psychotic users, ten patients did not perform the adapted Dixon's questionnaire. Therefore, the final groups consisted of 48 patients and 48 controls. There were no socio-demographic or psychopathological significant differences between those first-episode cannabis users who performed and those who did not performed the questionnaire. Socio-demographic characteristics of the final sample are shown in Table 3. A significantly greater proportion of psychotic patients than controls reported "to arrange my thoughts" as a reason to use cannabis. Moreover, significantly more patients than controls listed "to decrease my hallucinations and suspiciousness". These results are shown in Table 4.

4. Discussion

The main findings of the present study are: firstly, cannabis users have an earlier age of psychosis onset than non-users. Furthermore, the differential reasons to use cannabis for patients with

Table 4

Reasons for cannabis use in patients with psychosis and controls (non-psychotic cannabis users).

Reasons as shown in questionnaire	Patients with psychosis (%)	Controls (%)	χ^2	<i>P</i>
Relax	87.5	95.8	2.18	0.14
To be high	47.9	66.7	3.45	0.06
Increase the feeling of pleasure	50.0	30.6	1.05	0.31
Sleep better	50.0	62.5	2.86	0.40
Reduce boredom	60.4	58.3	0.04	0.84
Increase the intensity of emotions and feelings	29.2	18.8	1.43	0.23
To be more creative	41.7	41.7	0.00	1.00
Satisfy curiosity	31.3	39.6	0.73	0.52
Reduce feelings of sadness and depression	43.8	43.8	0.00	1.00
Go along with the group	33.3	35.4	0.46	0.83
Arrange my thoughts	29.2	10.4	5.32	0.02
Work better	12.5	10.4	0.10	0.75
Increase energy	12.5	2.7	3.65	0.06
Concentrate better on some things	27.1	18.8	0.94	0.33
Talk better to others	14.6	6.3	1.78	0.18
Decrease my hallucinations and suspiciousness	12.5	0.0	6.40	0.01

psychosis with respect to non-psychotic users are to arrange their thoughts and deal with hallucinations and suspiciousness.

The finding of an earlier age of psychosis onset in cannabis users is in accordance with previous meta-analyses (Large et al., 2011; Myles et al., 2012). One could think this may have been influenced by the gender difference in cannabis users, as women usually have a later psychosis onset (Dickerson, 2007). However, the multiple regression analysis indicated that both male gender and cannabis use were associated with earlier age at psychosis onset. Despite the consistent reporting of earlier age at psychosis onset in cannabis users, the exact reason for this has not yet been established (Myles et al., 2012), and the design of the present study does not allow us to test causality. An increase in cannabinoid CB1 receptors density in prefrontal areas during adolescence has been proposed to be responsible for this relationship in vulnerable individuals (Caballero and Tseng, 2012), as not all cannabis users develop psychosis. In this sense, Caspi et al. indicated that only those adolescent cannabis users who were Val carriers of the COMT Val158Met polymorphism, had an earlier age of psychosis onset (Caspi et al., 2005).

We found DUP was shorter in cannabis users than in non-users. This finding is in agreement with some authors (Burns, 2012; Burns et al., 2010), although other authors have found longer DUP in cannabis users (Broussard et al., 2013). These discrepancies could be due to cannabis use assessment (lifetime vs current), as some authors have already suggested (Burns, 2012). Nevertheless, despite the relationship between cannabis use and DUP, earlier psychosis onset was not just secondary to a shorter DUP, as Compton et al. proposed (Compton et al., 2009), because cannabis use predicted age at onset after taking into account DUP in the multiple regression analysis.

On the other hand, we were not able to distinguish differing characteristics of symptomatology between cannabis users and non-users. Although cannabis use has been related to persistent positive symptoms and relapses (Linszen et al., 1994; Schimmelmann et al., 2012), others authors have also failed to find PANSS positive differences between consumers and non-consumers (van Dijk et al., 2012), and after discontinuation of cannabis use (Barrowclough et al., 2013). It could be due to methodological aspects. Interestingly, one study that analyzed PANSS subitems found that cannabis use was associated with higher scores in conceptual disorganization and excitement (Stone et al., 2014). We were unable to carry out PANSS subitem analysis, but further studies clarifying this issue would be necessary.

Concerning reasons for cannabis use, the most common reasons for cannabis use were “to relax,” “reduce boredom,” and “to be high,” consistent with previous reports (Gomez Perez et al., 2014). With respect to the different reasons between psychotic and non-psychotic users, we found that cannabis was used specifically in psychotic patients to arrange their thoughts and decrease hallucinations and suspiciousness. These findings also support the self-medication hypothesis, as conceptual disorganization (Brune and Schaub, 2012), hallucinations and delusions are common symptoms in psychosis (Beavan and Read, 2010). To explain all our findings, we could speculate that in some patients, prodromal symptomatology began, for instance, suspiciousness, and patients took cannabis to relieve it. Nevertheless, contrary to their expectations, cannabis triggered full-blown psychosis. However, that is just a speculation, as the present study does not allow us to test that.

Regarding previous studies that compared reasons of cannabis use in patients with psychosis with a control group, the study by Saddicha et al. was carried out with a very different methodology. They assessed reasons of cannabis use with an open interview and divided reasons into external loci or internal loci (without specifying reasons).

They found that patients with psychosis tended to use cannabis for internal reasons (such as enhance positive mood) whereas subjects without psychosis used it for external reasons (such as work). Concerning the other articles that used a control group (Green et al., 2004; Schaub et al., 2008), they both found boredom was a distinguishing reason to use cannabis among patients with psychosis. Differences in methodology could help to explain these discrepancies. In our study, 12.5% of our patients used cannabis to decrease hallucinations and suspiciousness. In Green et al. study, they found 4.4% of patients used cannabis to deal with psychotic symptoms and Schaub et al. found that 19.3% of patients reported using cannabis to deal with hallucinations. However, they did not compare this item with the control group. As the presence of psychotic symptoms has been extensively described in the general population (Rossler et al., 2007), we included this item in our analysis. Moreover, reasons of cannabis use were assessed with a questionnaire similar to ours only in the study by Schaub et al.

Additionally, our study included first-episode psychosis patients, whereas the study by Schaub et al. and Green et al. included schizophrenia patients in different illness stages with different illness characteristics (Lewis and Lieberman, 2000). Furthermore, the variations of insight throughout different illness stages is an important consideration (Gerretsen et al., 2014), as first episode patients may be less able to recognize that they use cannabis to ameliorate their symptoms.

Despite efforts to overcome limitations in previous reports, the present study is not without its own limitations. DUP was obtained retrospectively and based on medical reports and clinical interviews, which may be inaccurate. However, it is important to highlight that clinical interviews of patients and relatives were performed by the patients' treating psychiatrists who had extensive experience treating Schizophrenia. Data regarding cannabis use was also assessed retrospectively; therefore we cannot discard recall bias. Furthermore, we were not able to distinguish the type of cannabis patients were using, and this fact could have influenced our results, as some authors have found an even greater risk of psychosis with high potency cannabis (Di Forti et al., 2014). Although the sample size was equivalent to, or larger than, previous studies, it may have been insufficient to accurately assess the reasons of cannabis use. Furthermore, we could not evaluate the reasons of cannabis use in the ten patients who did not perform the questionnaire, though their baseline variables were not significantly different from those who did perform the questionnaire. On the other hand, the questionnaire employed, although the most frequently used in previous studies, is not validated and utilizes excessively direct language, especially for positive psychotic symptoms, which could influence the frequency to which certain reasons are chosen.

In conclusion, our findings indicate that cannabis use is related to an earlier age at onset in patients with psychosis. Additionally, patients with first-episode psychosis report that they use cannabis to alleviate hallucinations, suspiciousness and to arrange their thoughts. These findings are in agreement with both hypotheses: self-medication and secondary psychosis hypothesis. However, longitudinal prospective cohort studies with better tools to assess reasons of cannabis use, will be the best scenario to investigate both hypotheses and their complementarity, studying factors associated to the development and maintenance of cannabis use and psychosis, to be able to develop appropriate treatment strategies in the future.

Funding

There was no external funding source.

Conflict of interest

The authors have no conflicts of interest to declare.

References

- Addington, J., Duchak, V., 1997. Reasons for substance use in schizophrenia. *Acta Psychiatr. Scand.* 96 (5), 329–333.
- Amorim, P., Lecrubier, Y., Weiller, E., Hergueta, T., Sheehan, D., 1998. DSM-IV-R Psychotic Disorders: procedural validity of the Mini International Neuropsychiatric Interview (MINI). Concordance and causes for discordance with the CIDI. *Eur. Psychiatry* 13 (1), 26–34.
- Andreasson, S., Allebeck, P., Rydberg, U., 1989. Schizophrenia in users and nonusers of cannabis. A longitudinal study in Stockholm County. *Acta Psychiatr. Scand.* 79 (5), 505–510.
- Archie, S., Boydell, K.M., Stasiulis, E., Volpe, T., Gladstone, B.M., 2013. Reflections of young people who have had a first episode of psychosis: what attracted them to use alcohol and illicit drugs? *Early Interv. Psychiatry* 7 (2), 193–199.
- Barnes, T.R., Mutsatsa, S.H., Hutton, S.B., Watt, H.C., Joyce, E.M., 2006. Comorbid substance use and age at onset of schizophrenia. *Br. J. Psychiatry* 188, 237–242.
- Barrowclough, C., Emsley, R., Eisner, E., Beardmore, R., Wykes, T., 2013. Does change in cannabis use in established psychosis affect clinical outcome? *Schizophr. Bull.* 39 (2), 339–348.
- Beavan, V., Read, J., 2010. Hearing voices and listening to what they say: the importance of voice content in understanding and working with distressing voices. *J. Nerv. Ment. Dis.* 198 (3), 201–205.
- Broussard, B., Kelley, M.E., Wan, C.R., Cristofaro, S.L., Crisafio, A., Haggard, P.J., Myers, N.L., Reed, T., Compton, M.T., 2013. Demographic, socio-environmental, and substance-related predictors of duration of untreated psychosis (DUP). *Schizophr. Res.* 148 (1–3), 93–98.
- Brune, M., Schaub, D., 2012. Mental state attribution in schizophrenia: what distinguishes patients with “poor” from patients with “fair” mentalising skills? *Eur. Psychiatry* 27 (5), 358–364.
- Burns, J.K., Jhazbhay, K., Emsley, R., 2010. Cannabis use predicts shorter duration of untreated psychosis and lower levels of negative symptoms in first-episode psychosis: a South African study. *Afr. J. Psychiatry* 13 (5), 395–399.
- Burns, J.K., 2012. Cannabis use and duration of untreated psychosis: a systematic review and meta-analysis. *Curr. Pharm. Des.* 18 (32), 5093–5104.
- Caballero, A., Tseng, K.Y., 2012. Association of cannabis use during adolescence, prefrontal CB1 receptor signaling, and schizophrenia. *Front. Pharmacol.* 3, 101.
- Caspi, A., Moffitt, T.E., Cannon, M., McClay, J., Murray, R., Harrington, H., Taylor, A., Arseneault, L., Williams, B., Braithwaite, A., Poulton, R., Craig, I.W., 2005. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biol. Psychiatry* 57 (10), 1117–1127.
- Compton, M.T., Kelley, M.E., Ramsay, C.E., Pringle, M., Goulding, S.M., Esterberg, M. L., Stewart, T., Walker, E.F., 2009. Association of pre-onset cannabis, alcohol, and tobacco use with age at onset of prodrome and age at onset of psychosis in first-episode patients. *Am. J. Psychiatry* 166 (11), 1251–1257.
- Di Forti, M., Sallis, H., Allegri, F., Trotta, A., Ferraro, L., Stilo, S.A., Marconi, A., La Cascia, C., Reis Marques, T., Pariante, C., Dazzan, P., Mondelli, V., Paparelli, A., Kolliakou, A., Prata, D., Gaughran, F., David, A.S., Morgan, C., Stahl, D., Khondoker, M., MacCabe, J.H., Murray, R.M., 2014. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophr. Bull.* 40 (6), 1509–1517.
- Dickerson, F.B., 2007. Women, aging, and schizophrenia. *J. Women Aging* 19 (1–2), 49–61.
- Dixon, L., Haas, G., Weiden, P.J., Sweeney, J., Frances, A.J., 1991. Drug abuse in schizophrenic patients: clinical correlates and reasons for use. *Am. J. Psychiatry* 148 (2), 224–230.
- Fowler, L.L., Carr, V.J., Carter, N.T., Lewin, T.J., 1998. Patterns of current and lifetime substance use in schizophrenia. *Schizophr. Bull.* 24 (3), 443–455.
- Gerretsen, P., Plitman, E., Rajji, T.K., Graff-Guerrero, A., 2014. The effects of aging on insight into illness in schizophrenia: a review. *Int. J. Geriatr. Psychiatry* 29 (11), 1145–1161.
- Gomez Perez, L., Santacana, A.M., Berge Baquero, D., Perez-Sola, V., 2014. Reasons and subjective effects of cannabis use among people with psychotic disorders: a systematic review. *Actas Esp. Psiquiatr.* 42 (2), 83–90.
- Goswami, S., Mattoo, S.K., Basu, D., Singh, G., 2004. Substance-abusing schizophrenics: do they self-medicate? *Am. J. Addict.* 13 (2), 139–150.
- Grech, A., Van Os, J., Jones, P.B., Lewis, S.W., Murray, R.M., 2005. Cannabis use and outcome of recent onset psychosis. *Eur. Psychiatry* 20 (4), 349–353.
- Green, B., Kavanagh, D.J., Young, R.M., 2004. Reasons for cannabis use in men with and without psychosis. *Drug Alcohol Rev.* 23 (4), 445–453.
- Haberstick, B.C., Young, S.E., Zeiger, J.S., Lessem, J.M., Hewitt, J.K., Hopfer, C.J., 2014. Prevalence and correlates of alcohol and cannabis use disorders in the United States: results from the national longitudinal study of adolescent health. *Drug Alcohol Depend.* 136, 158–161.
- Kay, S.R., Fiszbein, A., Vital-Herne, M., Fuentes, L.S., 1990. The Positive and Negative Syndrome Scale—Spanish adaptation. *J. Nerv. Ment. Dis.* 178 (8), 510–517.
- Khantzian, E.J., 1985. The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *Am. J. Psychiatry* 142 (11), 1259–1264.
- Khantzian, E.J., 1997. The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. *Harv. Rev. Psychiatry* 4 (5), 231–244.
- Kolliakou, A., Castle, D., Sallis, H., Joseph, C., O'Connor, J., Wiffen, B., Gayer-Anderson, C., McQueen, G., Taylor, H., Bonaccorso, S., Gaughran, F., Smith, S., Greenwood, K., Murray, R.M., Di Forti, M., Atakan, Z., Ismail, K., 2015. Reasons for cannabis use in first-episode psychosis: does strength of endorsement change over 12 months? *Eur. Psychiatry* 30 (1), 152–159.
- Koskinen, J., Lohonen, J., Koponen, H., Isohanni, M., Miettunen, J., 2010. Rate of cannabis use disorders in clinical samples of patients with schizophrenia: a meta-analysis. *Schizophr. Bull.* 36 (6), 1115–1130.
- Large, M., Sharma, S., Compton, M.T., Slade, T., Nielssen, O., 2011. Cannabis use and earlier onset of psychosis: a systematic meta-analysis. *Arch. Gen. Psychiatry* 68 (6), 555–561.
- Lewis, D.A., Lieberman, J.A., 2000. Catching up on schizophrenia: natural history and neurobiology. *Neuron* 28 (2), 325–334.
- Linszen, D.H., Dingemans, P.M., Lenior, M.E., 1994. Cannabis abuse and the course of recent-onset schizophrenic disorders. *Arch. Gen. Psychiatry* 51 (4), 273–279.
- Moore, T.H., Zammit, S., Lingford-Hughes, A., Barnes, T.R., Jones, P.B., Burke, M., Lewis, G., 2007. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* 370 (9584), 319–328.
- Myles, N., Newall, H., Nielssen, O., Large, M., 2012. The association between cannabis use and earlier age at onset of schizophrenia and other psychoses: meta-analysis of possible confounding factors. *Curr. Pharm. Des.* 18 (32), 5055–5069.
- Rössler, W., Riecher-Rössler, A., Angst, J., Murray, R., Gamma, A., Eich, D., van Os, J., Gross, V.A., 2007. Psychotic experiences in the general population: a twenty-year prospective community study. *Schizophr. Res.* 92 (1–3), 1–14.
- Saddichha, S., Prakash, R., Sinha, B.N., Khess, C.R., 2010. Perceived reasons for and consequences of substance abuse among patients with psychosis. *Prim. Care Companion J. Clin. Psychiatry* 12, 5.
- Schaub, M., Fanghaenel, K., Stohler, R., 2008. Reasons for cannabis use: patients with schizophrenia versus matched healthy controls. *Aust. N. Z. J. Psychiatry* 42 (12), 1060–1065.
- Schimmelmann, B.G., Conus, P., Cotton, S., Kupferschmid, S., McGorry, P.D., Lambert, M., 2012. Prevalence and impact of cannabis use disorders in adolescents with early onset first episode psychosis. *Eur. Psychiatry* 27 (6), 463–469.
- Schneier, F.R., Siris, S.G., 1987. A review of psychoactive substance use and abuse in schizophrenia. *Patterns of drug choice.* *J. Nerv. Ment. Dis.* 175 (11), 641–652.
- Schofield, D., Tennant, C., Nash, L., Degenhardt, L., Cornish, A., Hobbs, C., Brennan, G., 2006. Reasons for cannabis use in psychosis. *Aust. N. Z. J. Psychiatry* 40 (6–7), 570–574.
- Semple, D.M., McIntosh, A.M., Lawrie, S.M., 2005. Cannabis as a risk factor for psychosis: systematic review. *J. Psychopharmacol.* 19 (2), 187–194.
- Spencer, C., Castle, D., Michie, P.T., 2002. Motivations that maintain substance use among individuals with psychotic disorders. *Schizophr. Bull.* 28 (2), 233–247.
- Stone, J.M., Fisher, H.L., Major, B., Chisholm, B., Woolley, J., Lawrence, J., Rahaman, N., Joyce, J., Hinton, M., Johnson, S., Young, A.H., 2014. Cannabis use and first-episode psychosis: relationship with manic and psychotic symptoms, and with age at presentation. *Psychol. Med.* 44 (3), 499–506.
- van Dijk, D., Koeter, M.W., Hijman, R., Kahn, R.S., van den Brink, W., 2012. Effect of cannabis use on the course of schizophrenia in male patients: a prospective cohort study. *Schizophr. Res.* 137 (1–3), 50–57.
- Warner, R., Taylor, D., Wright, J., Sloat, A., Springett, G., Arnold, S., Weinberg, H., 1994. Substance use among the mentally ill: prevalence, reasons for use, and effects on illness. *Am. J. Orthopsychiatry* 64 (1), 30–39.