

# Cannabis and Bipolar Disorder: An Updated Look

---

Hurtado P.<sup>1</sup>, Kattan C.<sup>1</sup>, Urzúa G.<sup>1</sup>, Ivanovic-Zuvic F.<sup>2</sup>

## ABSTRACT

Both bipolar disorder and mental health disorders caused by substance abuse are frequently found in daily clinical practice. The consequences of cannabis use and its relationship to bipolar disorder have been the focus of research in recent years. The objective of this review is to evaluate the available evidence regarding the interactions between the use of cannabis and bipolar disorder. Epidemiological studies and research have shown that the frequency of cannabis use in patients with bipolar disorder is higher than in the general population. Over time, this comorbidity has been shown to be directly related to long-term deleterious effects, leading to an earlier onset of the mood disorder, more frequent and prolonged episodes, lower response to treatment, lower quality of life, and increased risk of suicide.

In this context, it is necessary to have comprehensive treatment for patients with bipolar disorder. It is of vital importance to focus the treatment on the prevention and discontinuation of consumption, actively treat comorbidity by the use of cannabis,

improve the results of the treatments, and achieve an improvement in the quality of life of our patients.

**Keywords:** cannabis, marijuana, bipolar disorder, mania

## INTRODUCTION

Bipolar disorder, as well as disorders caused by substance abuse, are mental health pathologies frequently found in daily clinical practice.

Currently, the use of cannabis has received significant attention, incrementally increasing its popularity in the general population and registering a considerable increase in its consumption. Regarding this matter, many countries have examined initiatives to legislate and consider the legalization of this substance. In this context, the discussion about the political, legal, social, and medical/clinical aspects related to its use becomes relevant <sup>(1)</sup>.

As for psychiatry, throughout its history, and especially in the past few years, the consequences of cannabis consumption and its relation to bipolar disorder have become a relevant focus of clinical research. The correlation among the multiple clinical aspects of bipolar disorder and the use of cannabis is, currently, of great interest.

A 2016 survey conducted by the National Service of Drug and Alcohol Use Prevention and Rehabilitation (SENDA) showed a prevalence of marijuana consumption in

---

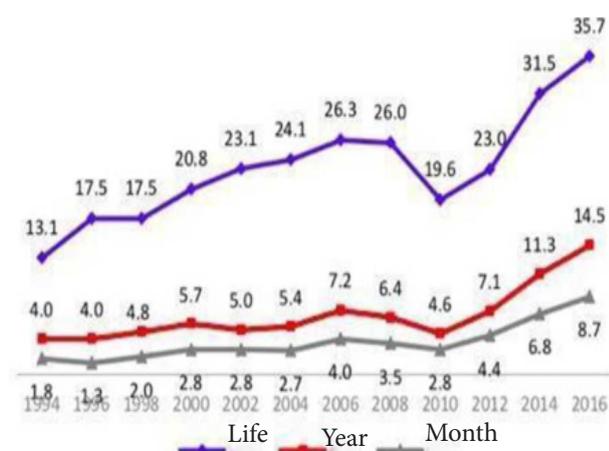
Received: October 2018

Accepted: December 2018

1.- Clinical Psychiatry Resident, School of Medicine, Clinical Hospital, Universidad de Chile

2.- Psychiatrist, University Psychiatric Clinic, School of Medicine, Clinical Hospital, Universidad de Chile

the past year of up to 14.5%. This shows an increase of 215.2% from the number registered in 2010, which corresponds to the year with the lowest prevalence in the past 20 years. Additionally, the prevalence of life consumption of cannabis is evidenced, which reached up to 35.7%, becoming the highest life prevalence registered in the past 20 years. It is important to note that this number represents an increase of 16% from 2010 <sup>(1)</sup>.



**Graphic No. 1:** twenty-second national study of drugs in the national population of Chile, 2016. senda.

Statistics obtained from the Irish population with bipolar disorder, after a twelve-month follow-up, evidenced a rate of cannabis use disorder of 7.2%. This number, in comparison with the 1.2% registered in the general population, reveal a clear association between marijuana consumption and bipolar disorder <sup>(2)</sup>.

A meta-analysis performed by the University of Cincinnati College of Medicine evidenced a fluctuating prevalence (between 5.6% and 46%) for cannabis use disorder in different cohorts. Remarkably the highest life prevalence is present in bipolar disorder type I, fluctuating between 19% and 46% <sup>(3)</sup>.

Among mood disorders, the ones that

show the highest comorbidity with cannabis use disorders correspond to clinical cases manifesting manic episodes. A prevalence of up to 40% for bipolar disorder type I and 20% for type II is evidenced. It is important to highlight that the lifetime prevalence of cannabis consumption reaches up to 70% in bipolar patients <sup>(4)</sup>.

These strong associations demand a critical view in light of an evident health problem, and, thus, to clarify its real implication in the evolution and prognosis of bipolar disorder.

## MATERIAL AND METHOD

This article was prepared by performing a bibliographical revision using MEDLINE's database through Pubmed's online search engine. The goal of the online search was to analyze the impact of cannabis consumption and its relation to bipolar disorder. The keywords used were "cannabis," "bipolar," "disorder," "induced," and "onset." Fourteen articles relating to the use of cannabis and bipolar disorder were found and reviewed.

Included among the eligibility criteria are reviews, studies, and meta-analysis from 2006 to date, limited to the search term "clinical trials," or clinical queries." Only extensive texts". were considered, contributing to the bibliography of the Psychiatric Clinic of the University of Chile. Works still in the process of research or publication were not included.

The review of these studies was performed taking into consideration the onset of the bipolar disorder, the age of onset, its relation to the type of mood episodes (mania or hypomania, depression, mixed episodes, psychotic symptoms, and rapid cycling), frequency and duration of the mood episode, the clinical stages of recovery, remission, relapses and recurrences,

cognitive disturbances, and suicidality.

## RESULTS

During the bibliographical revision, relevant information pertaining to the consumption of cannabis and its relations to certain aspects of bipolar disorder was found. Among the noteworthy aspects to be considered are its relation to incidence of mood disturbances; age of onset; its duration, type, and frequency of mood phases; its implications in the recovery, remissions, relapse, and recurrence of the disorder; its association with potential cognitive disturbances and its implications and relevance with suicidal episodes.

### ***Incidence of mood disorders and cannabis consumption***

In this area, the Netherlands National Institute of Mental Health and Addictions (NNIMHA), provides relevant information. Its three-year-long prospective study (1197;1998;1999) monitoring adult population from 18 to 64 years old, conducted on 3,881 subjects who did not have mood disorders and 3,854 subjects who did not have anxiety disorders, found associations between the consumption of cannabis and its incidence in depression and bipolar disorder.

The assessment instrument used was the Composite International Diagnostic Interview (CIDI, computerized version 1.1) and the data used was obtained from the Netherlands Mental Health Survey and Incidence Study NEMESIS. It was observed that the weekly, or more frequent, -use of cannabis -is associated with more than twice the risk of “any mood disorders” appearing from the first time. This relationship turned out to be stronger for bipolar disorder <sup>(5)</sup>.

### ***Incidence of mood disorders and cannabis consumption***

In this area, the Netherlands National Institute of Mental Health and Addictions (NNIMHA), provides relevant information. Its three-year-long prospective study (1197;1998;1999) monitoring adult population from 18 to 64 years old, conducted on 3,881 subjects who did not have mood disorders and 3,854 subjects who did not have anxiety disorders, found associations between the consumption of cannabis and its incidence in depression and bipolar disorder. The assessment instrument used was the Composite International Diagnostic Interview (CIDI, computerized version 1.1) and the data used was obtained from the Netherlands Mental Health Survey and Incidence Study NEMESIS. It was observed that the weekly, or more frequent, -use of cannabis -is associated with more than twice the risk of “any mood disorders” appearing from the first time. This relationship turned out to be stronger for bipolar disorder <sup>(5)</sup>

### ***Age of Onset***

In relation to this variable, from the articles reviewed, “The Use of Cannabis as Predictor of Early Onset of Bipolar Disorder and Suicide Attempts” is noteworthy. This review, performed in PubMed, takes into consideration articles published from 1948 until 2014 and compiles information relevant to the age of onset. Using keywords such as “bipolar disorder,” “suicide,” “suicide attempt,” “cannabis,” “marijuana,” “early age onset,” and “early-onset,” the following results were obtained: Cannabis consumption may trigger manic symptoms independent of age, ethnic background, sex, educational level, marital status, and the use of other drugs or alcohol.

Another article to consider, corresponds to the work of Van Laar et al. Its three-year

**Table 1.** Associations between cannabis consumption at the beginning of the study and the incidence of mood disorders after three years in accordance with the frequency of use during the period of highest usage.

Frequency of use	Any mood disorder	Major depression	Dysthymia	Bipolar Disorder
	OR {95% CI)	OR {95% CI)	OR {95% CI)	OR {95% CI)
Without use	1	1	1	1
1-3 per month	1.38 (0.70-2.71)	1.49 (0.82 - 2.71)	1.03 (0.28-3.74)	2.85 (0.56 -14.53)
1-4 days per month	2.57 (1.33-4.98)	1.79 (0.94 - 3.40)	2.27 (0.72 - 7.23)	8.93 (2.77 - 28.82)
Almost every day	2.38 (1.09 - 5.19)	1.60 (0.75 - 3.42)	1.54 (0.37 - 6.46)	3.13 (0.56-17.47)

The values are given as odd ratios (confidence intervals of 95%) using those subjects who did not inform any use of cannabis as a baseline. The numbers in bold indicate significant associations. Significance levels:  $P < 0.001$ ;  $P < 0.01$ ;  $P < 0.05$ . Adjusted per gender, age, education, location, employment, marital status, neuroticism, parent's psychiatric history, childhood traumatic events, life alcohol use and other disorders due to substance abuse, psychotic episodes, and anxiety disorders at the beginning of the study.

The frequency of cannabis use significantly increases the risks of exhibiting manic symptoms. Patients that used it 3-4 days per week were more likely to manifest manic symptoms than those who used it less frequently. In Bipolar disorders type I and II, the consumption of cannabis was associated with an earlier age of onset, independent of the history of psychosis or polarity of the first episode <sup>(6)</sup>.

A second systemic revision, entitled "Cannabis use and the first manic episode" <sup>(4)</sup>, provides relevant information for this aspect. The article is based on the search of information in Medline and PsychInfo, using "the following keywords: first manic episode, or onset mania, or bipolar disorder and cannabis. 163 articles published between 1972 and December 2013 were compiled, of which 53 studies were considered relevant.

In adults, the consumption of cannabis was correlated to the increase of more than twice the risk of suffering "any mood disturbance." This correlation was stronger for bipolar disorder, with an OR of 4.98 <sup>(5)</sup>. Associated with this, and in the context

of cannabis abuse, the beginning of depressive or manic episodes at an earlier onset is described <sup>(7;8)</sup>. Additionally, a clear association between the appearance of manic symptoms and the consumption of cannabis was observed, becoming a risk factor to be considered in the appearance of affective bipolar disorder <sup>(9)</sup>.

Any type of cannabis use predicted an increase in the risk of first bipolar disorder (OR 4.98, CI 95% 1.8-13.8). The risk of appearance of any other mood disorder was elevated for weekly and almost-daily users, but not for those who used it less frequently. It is shown that the comparison of patients with cannabis use disorders (with use in the past 12 months) versus those without a history of use, the age of onset decreases from 25.1 years old to 19.5 years old, and the age of the first depressive episode from 24.4 years old to 18.5. Associated with this, it is shown that in the group of cannabis users, the number of episodes per year (depressive, manic or hypo-manic) increases from 0.7 to 1.8 episodes <sup>(5)</sup>.

Table 2 Frequency of cannabis use in bipolar disorder

Study	Design	Sample (N)	Monitoring (years)	Measurements	Comparisons	Frequency of cannabis use
Henquet et al., 2006.	Cohort	4,815 subjects from 18 to 64 years old, a	3	Composite International Diagnostic Interview (CIDI).	The consumption of cannabis was correlated to the appearance of mania during clinical monitoring.	At least once a month; 1-3 days per month; 1-2 days per week; 3-4 days per week and almost every day.
Tijssen et al., 2010.	Cohort	705 patients from 14 to 24 years old.	8	Munich-Compo site International Diagnostic Interview (M-CIDI).	The onset of psychotic/depressive symptoms was evaluated with the following risk factors (family history of mood disorders, trauma, substance use, attention deficit disorder/hyperactivity (ADHD) and personality traits/temperament).	The life consumption of cannabis was considered as such if it was reported to be used five or more times at the beginning of the study.
Hert et al., 2011.	Transversal.	766 patients (676 with schizophrenia and 90 with bipolar disorder) from 16 to 65 years old	-	Composite International Diagnostic Interview (CIDI), Clinical Global Impression (CGI), and Global Assessment of Functioning (GAF).	A lineal regression was performed between the age of onset, considering the following variables: cannabis consumption, diagnostic, and gender.	Using CIDI for the life long use of substances, patients was classified as "intense users" when consumption occurred several times a day.
Lagerberg et al., 2011.	Transversal.	151 patients with bipolar disorders (91 BP I and 60 BP II).	-	Clinical evaluations performed by clinical psychologist and psychiatrists.	Bivariate analysis revealed significant correlations between the age of onset and gender, age, type of BP, excessive cannabis consumption, and sequence.	Patients who complied with the DSM-IV criteria for substance abuse disturbances or who consumed cannabis weekly during a period of four years, for the age range of 11 to 15, 16 to 20, 21 to 27, 28 to 44, 45 to 60, and 60 years old were considered as "excessive consumption of cannabis."
LevRan et al., 2013.	Transversal.	1,905 patients with bipolar disorder	-	Structured interviews about alcohol consumption and related disabilities.	Cannabis use disorder (CUD) rates in the past 12 months were 7.2% in comparison to 1.2% in the general population. Logistical regression models adjusted to the socio-demographic variables showed that concurrent CUD had a higher risk of dependency than nicotine, alcohol and drug abuse disorders, and antisocial personality disorder in comparison to those who do not have CUD.	The number of cannabis cigarettes consumed and the number of days in which cannabis was used in the past 12 months. The frequency defined from "almost daily" to "once a year."

## **DURATION, TYPES, AND FREQUENCY OF MOOD STAGES**

From the articles analyzed, the work of Henquet et al. stands out. In this prospective study, the use of cannabis and mania, performed on 4,815 subjects and based on structured interviews, showed that the consumption of cannabis considerably increased the risk of manic symptoms during monitoring (OR 2.7; IC 95%, 1.54-4.75). The cases were adjusted per age, sex, educational level, ethnic group, marital status, neuroticism, other drug use, alcohol use, and depressive and manic symptoms at the time of the study <sup>(10)</sup>.

The association between the consumption of cannabis and mania was independent of the prevalence and incidence of psychotic symptoms. There was no evidence of inverse causality, as the manic symptoms at the beginning of the study did not predict the beginning of cannabis consumption during monitoring (OR=0.35%; IC 95%: 0.03 to 3.49) <sup>(10)</sup>.

The systematic revision performed by Gibbs et al. concluded that there are studies that support that the consumption of cannabis may worsen the onset of manic symptoms in persons previously diagnosed with bipolar disorder. The regression analysis revealed that the time of cannabis consumption was significantly associated with the duration of the manic episode <sup>(11)</sup>.

The consumption of cannabis may act as a causal risk factor in the incidence of manic symptoms. The results of the meta-analysis showed that the consumption of cannabis is associated with an almost tripled increased probability of presenting manic symptoms in the non-hospitalized population <sup>(11)</sup>.

Vik et al. offer a prospective study performed in patients diagnosed with bipolar disorder. The main finding was a dosage-response relationship between the consumption of cannabis and the age of onset of bipolar disorder. The effect of cannabis over the age of onset was independent of the polarity and psychotic symptoms; that is, it is present in bipolar disorder regardless of the initial stage and independent of the psychotic symptoms <sup>(12)</sup>.

## **RECOVERY, REMISSION, RELAPSE, AND RECURRENCE**

With respect to this aspect, the information is relevant and was obtained thanks to the research team of Zorrilla et al. in 2014. It corresponds to a two-year-long observational prospective study that monitored 530 researchers, 14 European countries and a total sample of 3,684 subjects that comply with the diagnostic of mixed manic/depressive bipolar disorder according to the criteria of the DSM-IV, CIE-10 or arbitrary clinical criteria. The scales used for the clinical evaluation were the following:

Clinical Global Impression Bipolar Disorder (CGI-BP), Young Mania Rating Scale (YMRS), and Hamilton Depression Rating Scale (HAMD-5). Said study aims to explore the long terms consequences of continuation or cessation of cannabis consumption, taking into consideration clinical aspects such as remission, recovery, recurrence and relapse in patients with bipolar disorder. The authors split the groups of patients diagnosed with bipolar disorder in three groups according to cannabis consumption. The groups correspond to patients who have never used cannabis, patients who have used it at some point in their lives, and the third group of current users <sup>(13)</sup>.

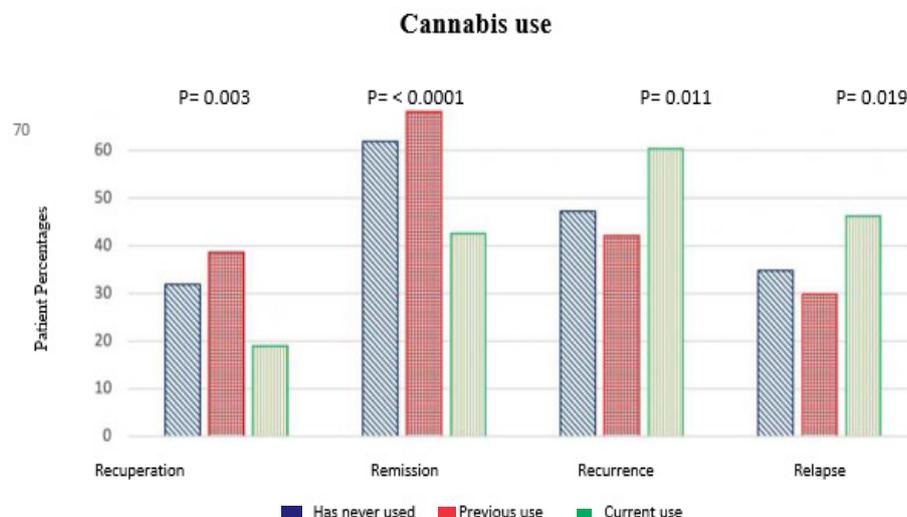
The results were expressed in a schematic graphic in the following manner:

In the group of patients with bipolar disorder who experimented recovery, 31.8% had never used cannabis, 38.7% presented previous use, and 18.9% were current users. With respect to the group of patients with bipolar disorder that achieved remission, there was 61.9% of patients who had never used cannabis, 68.1% who presented previous use, and 42.6% who were current users. With respect to the group of patients with bipolar disorder that suffered a recurrence, there was 47.3% of patients who had never used cannabis, 42.1% who presented previous use and 60.3% who were current users. The last group within the study--patients with bipolar disorder who suffered a relapse--stood out, with 34.9% of patients who had never used cannabis, 29.8% who presented previous use and 46.3% who were current users <sup>(13)</sup>.

Among the relevant conclusions, the authors state that the consumption of cannabis within the context of bipolar patients increase the symptoms of mania, shows worse compliance with drug treatments, leads to a worse quality of life, and shows a higher risk of hospitalization, a higher percentage of rapid cycling and more suicidal behaviors <sup>(13)</sup>.

For Sung-Wan Kim et al., based on this prospective observational study (24 monitoring) which included a sample of 239 patients with bipolar disorder type I and schizoaffective disorder, in which participants were classified as regular cannabis users (three or more times per week) or non-users and considered remission as the primary measure of results, reached the following conclusions:

The consumption of cannabis was significantly associated with a lower probability of remission during the 24 months of monitoring. The subgroup analysis showed that the consumption of cannabis was significantly associated with lower remission rates in the Hamilton Depression Classification Scale. The consumption of cannabis is significantly associated with lower remission rated in the Young qualification scale for mania. In conclusion, it is sustained that the use of cannabis negatively affects the long-term clinical results in patients in the spectrum of bipolar disorder. It requires a comprehensive evaluation and integrated management of the consumption of cannabis to obtain better treatment results for disorders in the bipolar spectrum. <sup>(14)</sup>



Another article to consider, corresponds to the work of Van Laar et al. Its three-year prospective study (1997; 1998; 1999) monitoring an adult population from 18 to 64 years old, performed on 3,881 subjects who did not show mood disturbances and 3,854 subject who did not present anxiety disorders, was able to show essential associations between the consumption of cannabis and the incidence of depression and bipolar disorder <sup>(5)</sup>

### **Rapid cycling and mixed episodes**

With respect to rapid cycling and mixed episodes, relevant information from different authors was found. For patients who consume cannabis, the deterioration and risk of rapid cycling increased considerably <sup>(7;15)</sup>. Also, it was noted that the risk of comorbidity due to substance abuse was higher for patients with rapid cycling than manic patients with mixed episodes <sup>(20; 21; 22)</sup>. Nevertheless, Agrawal et al. (2011) did not find a significant statistical increase in the risk of rapid cycling but did so in the risk of mixed episodes <sup>(23; 4)</sup>. With respect to the age of onset is rapid cycling, they found an OR of 2.0 <sup>(6)</sup>.

### **Suicide**

Bipolar disorder implies the risk of suicide as the leading cause of death among patients. It is estimated that among 25% and 50% of patients with bipolar disorder will attempt suicide at least once in their lifetimes and that 8% to 19% will consider suicide <sup>(16)</sup>.

In the EMBLEM study, the proportion patients with suicidal attempts during the maintenance stage (6 to 24 months) was higher in the group with current use of cannabis (9/130, 6.9%) than in the group that had never used it (51/17, 3.0%) and

the group with previous use of cannabis (4/90, 4.4%) (P= 0.046) <sup>(13)</sup>.

A Danish study, prospective and based on records by Ostergaard et al., proved that the associations among different disturbances due to substance use and suicidality in a large sample of subjects with grave mental illness. Individuals with TB and co-morbid substance use has a higher probability of having a history of suicidal attempts in comparison to their non-co-morbid cohorts (23.2% versus 10.2%). In their findings, Ostergaard showed that disturbances due to current cannabis consumption were associated with a higher risk of suicide [risk rate of (HR) 1.86; IC of 95% = 1.15–2.99], although not with suicidal attempts (HR = 0.93; IC of 95% = 0.76–1.13). The effect of cannabis consumption in death by suicide was estimated only among subjects with bipolar disorder, as there were no significant associations among persons who suffered schizophrenia, depression and other personality disorders <sup>(17)</sup>.

In any case, the following items still need clarification:

- 1) The consumption of cannabis has adverse effects on bipolar symptoms, which, conversely, may increase suicide risk.
- 2) People more gravely ill have a higher probability of controlling their symptoms using cannabis.
- 3) The vulnerability of the individual to both cannabis consumption as well as suicide, maybe due to a split factor, such as higher impulsivity levels.

## Cognitive function

It has been observed that the use of cannabis may be related to cognitive deficiencies in users, but there is little information about the neurocognitive effects in patients with bipolar disorder.

Braga and cols in a retrospective study observed that there is a better cognitive performance in bipolar patients who abuse cannabis compared to non-consumers. Ringen and cols also noted better verbal fluency among bipolar patients with co-morbid consumption. Increased performance may be related to better cognitive abilities necessary to procure and maintain the use of cannabis <sup>(18; 19)</sup>.

## CONCLUSIONS

Co-morbid use of cannabis is associated with an earlier age of onset and increases in manic, depressive, psychotic, and rapid cycling symptoms, along with lower compliance and worse performance.

Bipolar patients who stop consuming cannabis during a manic or mixed episode have similar clinical and performance results to those who have never consumed cannabis. Therefore patients who continue consuming cannabis have a higher risk of recurrence and worse performance.

A holistic managing plan for bipolar patients must include psycho-education and other treatments or interventions centered on the cessation of consuming cannabis, alcohol, and other drugs, as well as improving compliance and preventing relapse.

## BIBLIOGRAPHY

1. Décimo segundo estudio nacional de drogas en población general de Chile. SENDA, 2016.
2. Lev-Ran S, Le Foll B, Mc Kensie K, George T, Rehm J. Bipolar disorder, and co-occurring. Cannabis use disorders: Characteristics, co-morbidities and clinical correlates *Bipolar Res* 2013;209: 459-65.
3. Cerullo MA<sup>1</sup>, Strakowski SM. The prevalence and significance of substance use disorders in bipolar type I and II disorder. *Subst Abuse Treat Prev Policy* 2007;2:29.
4. Bally N, Zullino D, Aubry JM. Cannabis use and first manic episode. *J Affect Disord* 2014; 165: 103-8.
5. Van Laar M, Van Dorsselaer S, Monshouwer K, De Graaf R. Does cannabis use predict the first incidence of mood and anxiety disorders in the adult population? *Addiction* 2007; 102: 1251-60.
6. Leite RT, Nogueira Sde O, do Nascimento JP, de Lima LS, de Nobrega TB, Virginio Mda S et al. The Use of Cannabis as a Predictor of Early Onset of Bipolar Disorder and Suicide Attempts. *Neural Plast*, 2015;2015:434127.
7. Duffy A, Horrocks J, Milin R, Doucette S, Persson G, Grof P. Adolescent substance use disorder during the early stages of bipolar disorder: a prospective high-risk study. *J Affect Disord* 2012; 142:57-64.
8. Lagerberg, T. V., Sundet, K., Aminoff, S. R., Berg, A. O., Ringen, P. A., Andreassen, O. A., & Melle, I. (2011) Excessive cannabis use is associated

with earlier age at onset in bipolar disorder. *European archives of psychiatry and clinical neuroscience*, 261(6), 397–405.

9. Tjssen MJ, Van Os J, Wittchen HU, Lieb R, Beesdo K, Wichers M. Risk factors predicting onset and persistence of subthreshold expression of bipolar psychopathology among youth from the community. *Acta Psychiatr Scand*. 2010;122:255-66.
10. Henquet, C., Krabbendam, L., De Graaf, R., Ten Have, M., Van Os, J., 2006. Cannabis use and expression of mania in the general population. *J. Affect. Disord.* 95, 103–110.
11. Gibbs M1, Winsper C1, Marwaha S2, Gilbert E3, Broome M4, Singh SP1. Cannabis use and mania symptoms: a systematic review and meta-analysis. *J Affect Disord.* 2015 Jan 15;171:39-47. doi: 10.1016/j.jad.2014.09.016. Epub 2014 Sep 23.
12. Trine Vik Lagerberg, Levi Røstad Kvitland, Sofie R. Aminoff b, Monica Aas, Petter Andreas Ringen, Ole Andreas Andreassen, Ingrid Melle indications of a dose–response relationship between cannabis use and age at onset in bipolar disorder *Psychiatry Research* 215 (2014) 101–104
13. Zorrilla, I, Aguado, J, Haro, JM, Barbeito, S, López Zurbano, S, Ortiz, A, López, P, Gonzalez-Pinto, A. Cannabis and bipolar disorder: does quitting cannabis use during manic/mixed episode improve clinical/functional outcomes 2014
14. Sung-Wan Kim, Seetal Dodd, Lesley Berk, Jayashri Kulkarni, Anthony de Castella, Paul B. Fitzgerald, Jae-Min Kim, Jin-Sang Yoon and Michael Berk. 2015 Korean Neuropsychiatric Association. Impact of Cannabis Use on Long-Term Remission in Bipolar I and Schizoaffective Disorder.
15. Strakowski SM, DelBello MP, Fleck DE, Adler CM, Anthenelli RM, Keck PE, Arnold LM, Amicone J (2007) Effects of co-occurring cannabis use disorders on the course of bipolar disorder after a first hospitalization for mania. *Arch Gen Psychiatry* 64:57–64.
16. Marangell LB, Bauer MS, Dennehy EB, et al: Prospective predictors of suicide and suicide attempts in 1,556 patients with bipolar disorders followed for up to 2 years. *Bipolar Disord* 2006; 8:566-575.
17. Ostergaard, M. L. D., Nordentoft, M., and Hjorthoj, C. (2017) 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*, 112: 1250– 1259.
18. Ringen, P.A., Vaskinn, A., Sundet, K., Engh, J.A., Jonsdottir, H., Simonsen, C., Friis, S., Opjordsmoen, S., Melle, I., Andreassen, O.A., 2010. Opposite relationships between cannabis use and neurocognitive functioning in bipolar disorder and schizophrenia. *Psychol. Med.* 40, 1337–1347
19. Braga, R.J., Burdick, K.E., Derosse, P., Malhotra, A.K., 2012. Cognitive and clinical outcomes associated with cannabis use in patients with bipolar I disorder. *Psychiatry Res.* 200, 242–245

20. Himmelhoch, J.M., Mulla, D., Neil, J.F., Detre, T.P., Kupfer, D.J., 1976. Incidence and significance of mixed affective states in a bipolar population. *Arch. Gen. Psychiatry* 33, 1062–1066.
21. McElroy, S.L., Keck Jr., P.E., Pope Jr., H.G., Hudson, J.I., Faedda, G.L., Swann, A.C., 1992. Clinical and research implications of the diagnosis of dysphoric or mixed mania or hypomania. *Am. J. Psychiatry* 149, 1633–1644.
22. Sonne, S.C., Brady, K.T., Morton, W.A., 1994. Substance abuse and bipolar affective disorder. *J. Nerv. Ment. Dis.* 182, 349–352.
23. Agrawal, A., Nurnberger Jr., J.I., Lynskey, M.T., 2011. Cannabis involvement in individuals with bipolar disorder. *Psychiatry Res.* 185, 459–461.