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Impact of *Cannabis* Use Disorder on the Course and the Prognosis of Bipolar Disorder Type 1

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Abstract

Abstract: Objectives Bipolar Disorder (BD) is a psychiatric pathology marked by a significant socio-professional impact. Its comorbidity with other disorders would make the prognosis more severe. Addictive co-morbidities, particularly the *Cannabis* Use Disorder (CUD), are of great interest. The objective of our study was to determine the impact of cannabis use disorder on the course and prognosis of type 1 Bipolar Disorder (BD1).

Methods: This is a cross-sectional and comparative study carried out on 75 patients with Bipolar Disorder type 1 (BD1) including 30 with a comorbid *Cannabis* Use Disorder (CUD+ group) without any other substance use disorder, compared to 45 without *cannabis* or any other substance use disorder (CUD- group). The CUD was evaluated according to the DSM-V criteria. The euthymia was verified by the Hamilton depression and Young mania scales. Compliance was assessed by the Medication Adherence Rating Scale questionnaire, insight by the Q8 scale and functioning by the Global Functional Assessment scale.

Results: In our population of patients with BD1, CUD was associated with celibacy (p=0.021), residence in an urban area (p=0.013), professional instability (p=0.001) and a family dynamic marked by violence (p=0.04). CUD was also associated with tobacco use disorder (p=0.042), occasional alcohol consumption (p=0.001), personality disorders (p=0.003) especially the antisocial type (p=0.008), a history of stay abroad (p=0.008) and a criminal record (p = 0.016). Clinically and therapeutically, CUD was associated with more frequent manic relapses (p <0.001), poor insight (p<0.001), poor adherence to therapy (p=0.001), and prescription of antipsychotics long-acting (p=0.007) and benzodiazepines (p=0.036). The prognostic factors associated with CUD in a multivariate study and after adjusting for confounding variables were more frequent manic relapses (p<0.001; ORa=18; 95% CI 3.9-88), sub syndromic symptoms (p=0.007; ORa=3.7; 95% CI 1.4-9.8), more frequent hospitalizations (p<0.001; ORa=36; 95% CI 4.3-310) and more prolonged (p <0.001; ORa = 5; 95% CI 1.6-5.5), lack of socio-professional reintegration (p=0.001; ORa=5.3; 95% CI 1.5-14.6) and overall poor functioning (p=0.001; ORa=6,8; 95% CI 2-22.6).

Conclusion: Our study highlighted the deleterious impact of *cannabis* use disorder on the course and prognosis of bipolar disorder. Common in Tunisia and around the world, *cannabis* use disorder is a real scourge with negative consequences, especially on mental health. As a result, developing strategies for managing these comorbidities and developing international consensuses could constitute targets for curative actions and could have a positive impact on mental health.

Keywords

Bipolar disorder; *Cannabis*; Comorbidity; Abuse; Addiction; Course; Prognosis

Introduction

Bipolar Disorder (BD) is a common psychiatric condition. Its lifetime prevalence has been estimated at 1% [1]. This disorder is chronic, severe and complex. Its complexity lies in psychosocial and legal complications and co-morbidity with other psychiatric disorders [2]. Comorbidity between BD and substance use disorder is very common, with a high prevalence of substance use disorder in the order of 61% in Bipolar Disorder type 1 (BD1) and 48 % in type 2 compared to that of the general population (6%) [2]. Among psychoactive substances, cannabis is the most widely used psychoactive substance in BD with a prevalence reaching 47% [3,4]. In Tunisia, the prevalence of the consumption of psychoactive substances has increased in recent years [5]. For *cannabis*, in particular, the Mediterranean school Survey Project on Alcohol and other Drugs (MedSPAD) [6], carried out in Tunisia in 2013 and then in 2017, highlighted an increase in the prevalence of *cannabis* consumption passing from 1.5% in 2013 to 3.8% in 2017. Co-morbidity with the *Cannabis* Use Disorder (CUD) is at the origin of sometimes ambiguous clinical pictures leading to misdiagnosis with schizoaffective disorder, schizophrenia, personality disorders and other mood disorders [7]. Substance use disorder, including *cannabis*, can affect the course of bipolar disorder, its prognosis, response to therapy, and the quality of life of patients [8].

This is a hot topic and a research avenue. Indeed, few studies have assessed the impact of *cannabis* alone among psychoactive substances on the course of BD. At present, there is a lack of evidence available in international recommendations for treatment strategies for BD comorbidity with CUD. Indeed, determining the pathogenic and prognostic factors of this comorbidity could constitute targets for curative and preventive actions. It is from this perspective that we conducted our study, the objective of which was to assess the impact of CUD on the course and prognosis of BD1. To our knowledge, this is the first Tunisian study focusing specifically on the comorbidity between BD1 and CUD without disorders in the use of other psychoactive substances apart from tobacco, with control for confounding factors in multivariate analysis.

Methods

Type of study

We carried out a cross-sectional and comparative study in one of the psychiatry departments at Razi Hospital in La Manouba. Itis the only psychiatric hospital in Tunisia. The study was conducted over a seven-month period from June 1 to December 30, 2018, patients were recruited during post-hospitalization consultations. These are weekly consultations.

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Study population

We included male patients with BD1 according to DSM-5 criteria, followed for at least one year and who had been in thymic remission for at least three months. Patients with BD type other than type 1, nor those with diagnostic doubt or with cognitive or sensory impairment that could interfere with clinical assessment were not included. A total of 75 patients were included. The population was divided according to the presence or not of CUD. Thus, we had a first group of 30 patients with CUD associated according to the criteria of DSM-5, without notion of disorder of the use of other psychoactive substances except tobacco (CUD+ group) and a second group of 45 patients without any associated substance use disorder other than tobacco (CUD- group).

Measuring tools

Socio-demographic and clinical data and those related to *cannabis* use were collected from medical records and supplemented with patients. We used the Hamilton Depression Scale (HDRS) [9] and the Young Mania Scale (YMRS) [10] for euthymia assessment to include only patients with euthymia. We used the Medication Adherence Rating Scale (MARS) questionnaire [11] for compliance assessment. For the evaluation of insight, we used the (Q8) insight scale [12]. The operation was assessed by the Global Operating Assessment Scale (FGM) [13]. To minimize evaluation bias, the same investigator collected data, shifted scales, and entered data. The evaluation was done on the same day. All our patients gave their free and informed consents to participate in this study. The study was approved by the Tunis Medical School.

Statistical analysis

The data was captured and analyzed using IBM SPSS software® version 22. For the descriptive study, we calculated absolute frequencies and relative frequencies (percentages) for qualitative variables. We calculated averages, medians and standard deviations and determined the extreme values for quantitative variables. For the univariate analytical study, comparisons of independent series averages were made using the Student t test for independent series, and in the non-Gaussian distribution by the Mann and Whitney non-parametric test. Comparisons of percentages on independent series were made by the Pearson chi-two test. If this test was not valid, we used Fisher's exact bilateral test. We used a multivariate analysis to calculate Adjusted Odds Ratios (ORa), measuring the proper role of *cannabis*. The significance threshold in all statistical tests was 0.05.

Results

Descriptive study

Socio-demographic clinic and therapeutic characteristics of our study population: For the socio-demographic characteristics of our study population, the average age of our sample was 36.9/-9.6 years (34/-7.7 years in the CUD+ group versus 38.8-10.3 years in the CUD-group).) All our patients were male, 65% of whom were single (74% in the CUD+ group versus 60% in the CUD-group) (Table 1). Concerning the clinical and therapeutic characteristics of the study population, a family history of substance use disorders was observed in 9% of the total sample (13% of the CUD+ group versus 7% of the CUD-group). For the personal anntals, 19% of our patients had a history of staying abroad (33% of the CUD+ group vs 9% of the CUD-group). A personal criminal history has been recovered in 40% of our patients (57% of the CUD+ group versus 29% of the CUD-group). Clinically, an antisocial personality has been found in 7% of cases which were all from the CUD+ group (17%). The annual frequency of manic relapses in our sample was 0.5-0.4 (0.8-0.4 for the CUD+ group versus 0.4-0.2 of the CUD-group). The average annual frequency of depressive relapses in our sample was 0.18-0.2 (0.22-0.3 in the CUD+ group versus 0.16-0.2 in the CUD-group). We found complete remission in 57% of our patients ((40% of the CUD+ group versus 71% of the CUD- group). The insight was bad for 21% of patients in our series (43% of the CUD+ group versus 7% of the CUD-group). Thermoregulatory treatment regulator therapy was prescribed in all of our patients. The long-acting antipsychotics were prescribed to 28% of our sample (47% of the CUD+ group versus 16% of the CUD- group). Benzodiazepines were prescribed for 24% of the total sample (37% of the CUD+ group versus 16% of the CUD-group). The response to treatment during an acute episode was good in 69% of our patients (57% of the CUD+ group versus 78% of the CUD- group). On the MARS scale, the average compliance score in the patients in our sample was 6.6-2.1 (5.2-2.1 in the CUD+ group versus 7.5-1.6 in the CUD). For the CUD group, the average age of onset of cannabis use was 19.2-4.4 years. It chronologically preceded the onset of BD in 80% of CUD patients. The average duration of this consumption was 14.6-7.8 years.

The different evolutionary and prognostic characteristics associated with BD have been studied. Socio-professional integration was found in 60% of our patients (37% of the CUD+ group versus 76% of the CUD-group). We found complete remission in 57% of our patients (40% of the CUD+ group versus 71% of the CUD-group). The average annual frequency of hospitalizations for our sample was 0.5+/-0.4 (0.7+/-0.5 in the CUD+ group versus 0.4+/-0.2 in the CUD-group). The average length of hospitalizations per year for our sample was 9.9+/-7.8 days (13.6+/8.5 days for the CUD+ group versus 7.5+/-6.4 days in the CUD- group). The overall average operating score for our series was 67+/-13.7 (57+/-13 in the CUD group versus 74+/-9.3 in the CUD-group (Table 2).

Analytical study

Associations between socio-demographic clinic and therapeutic variables of patients with type 1 bipolar disorder and cannabis use disorder: We found a statistically significant association between the CUD and the following socio-demographic variables: occupational instability (p=0.001), urban residence (p=0.013), lack

Table 1: Breakdown of patients with BD1 by socio-demographic characteristics.

Socio-demographic variables	Total sample (N=75)	CUD Group (N=30)	CUD Group (N=45)
Age (years)	36,9 ± 9,6*	34 ± 7,7*	38,8 ± 10,3*
Single status	49 (65)	22 (74)	27 (60)
Residence in urban areas	53 (71)	26 (87)	27 (60)
Education level -Primary -Secondary	32 (43) 30 (40)	12 (40) 13 (43)	20 (44) 17 (38)
Lack of occupation	24 (32)	12 (40)	12 (27)
Occupational absenteeism	24 (32)	14 (47)	10 (22)
Socio-economic level -Medium -Down	44 (59) 26 (34)	15 (50) 11 (37)	29 (65) 15 (33)
Lack of family support	15 (20)	10 (33)	5 (11)
Relations intrafamilial disharmonious	17 (22)	11 (37)	6 (13)
Intrafamilial violence	14 (18)	9 (31)	5 (10)

*Average +/- type deviation; N: number of cases (percentage);
CUD+: BD1 with *Cannabis* use disorder; CUD-: BD1 without *Cannabis* use disorder

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of family support (p=0.018), lack of intra-family cohesion (p=0.018), single status (p=0.021) and domestic violence (p=0.04). Regarding the history of patients with BD1, we found a statistically significant association between CUD and the following variables: occasional alcohol consumption (p=0.001), the presence of a personality disorder (p=0.003), the presence of an antisocial personality disorder (p=0.008) and the presence of a smoking disorder (p=0.008), the presence of a personal criminal history (p=0.016) and the presence of a smoking disorder (p=0.042). Also, we found a statistically significant association between CUD and the following clinical variables: the annual frequency of manic episodes (p<0.001), the poor insight (p<0.001) and the persistence of sub syndromic thymic symptoms in free intervals (p=0.007). A statistically significant association between CUD and the following therapeutic variables was found: poor adherence (p=0.001), irregular follow-up (p=0.001), use of the long-acting antipsychotics (p=0.007), mode of forced hospitalization (p=0.019) and prescription of benzodiazepines (p=0.036).

Table 2: Breakdown of patient groups by evolutionary and prognostic characteristics.

Prognostic variables	Sample total N=75	Group CUD+ N=30	Group CUD- N=45
Socio-professional insertion	45 (60)	11 (37)	34 (76)
Partial remission in free intervals	31 (43)	18 (60)	23 (29)
Annual frequency of thymic relapses	0,8 ± 0,5*	1,1 ± 0,6*	0,6 ± 0,3*
Annual frequency of hospitalizations	0,7 ± 0,5 *	0,4 ± 0,2*	0,5 ± 0,4*
Average length of hospitalizations	9,9 ± 7,8*	13,6 ± 8,5*	7,5 ± 6,4*
Functionnement global	67 ± 13,7*	57 ± 13*	74 ± 9,3*

*Average +/- type deviation; N: number of cases (percentage).
CUD+: BD1 with *Cannabis* use disorder; CUD-: BD1 without *Cannabis* use disorder

Table 3: Associations between the evolutionary and prognostic characteristics of type 1 bipolar disorder and *Cannabis* use disorder.

Prognostic variables		CUD+ %	CUD- %	P	Univariate study OR (CI = 95%)	Study Multi-variate Now (CI=95%)
Socio-professional insertion	Absent	63	24	0,001	5,3 (1,5-14,6)	5,3 (1,5-14,6)
	This	37	76			
Quality of free intervals	Good	40	71	0,007	3,7 (1,4 -9,8)	3,7 (1,4-9,8)
	Bad	60	29			
Annual frequency of thymic relapses	≤ 0,65	14	60	<0,001	2,9 (2,3-27,2)	18 (3,9-88)
	>0,65	86	40			
Fast cycles	Present	13	4	0,21	3,3 (0,6-19,3)	NS
	Absent	87	96			
Annual frequency of hospitalization	≤ 0,56	10 (33)	78	<0,001	9,2 (3,1-27,1)	36 (4 -310)
	>0,56	67	22			
Length of hospitalizations per year in days	≤ 7,49	23	69	<0,001	7,2 (2,5 -0,9)	5 (1,6-15,5)
	>7,49	77	31			
Global operation	≤ 70	87	51	0,001	6,8 (2-22,6)	6,8 (2-22,6)
	>70	13	49			

CUD+: BD1 with *Cannabis* use disorder; CUD-: BD1 without a *Cannabis* use disorder; P: significance threshold; CI: Confidence Interval; NS: Not Significant; OR: Odds Ratio; ORa: adjusted Odds Ratio

Associations between the course and prognostic characteristics of type 1 bipolar disorder and cannabis use disorder

Univariate study: In univariate analysis, CUD was associated with the following prognostic elements: the annual frequency of maniac episodes (p<0.001), the annual frequency of hospitalizations (p<0.001), the average length of hospitalizations per year (p<0.001), a general malfunction (p=0.001), lack of socio-professional integration (p=0.001) and persistence of sub syndromic thymic symptoms in free intervals (p=0.007).

Multivariate study: We performed a logistic regression step-by-step approach for each of the prognostic elements to control the confounding variables (smoking disorder, occasional alcohol use, intrafamilial violence, civil status, and age at the time of study). After adjusting the confounding variables, CUD continues to be associated with the following prognostic elements: general malfunction, lack of socio-professional reintegration, the presence of sub syndromic thymic symptoms in free intervals, the annual frequency of maniac episodes and hospitalizations, and the average length of hospitalizations per year (Table 3).

Discussion

The CUD had a negative impact on the evolutionary course of BD1. We found that compared to patients with BD1 and CUD-, bipolar CUD+ patients had a worse insight (p<0.001), a higher annual frequency of manic relapses (p<0.001) and more subsyndromal thymic symptoms in free intervals (p=0.007). They also had poorer adherence (p=0.001), more irregular follow-up (p-0.001) with more frequent prescription of long-acting neuroleptics (p=0.007) and benzodiazepines (p=0.036) with a higher frequency of forced hospitalizations (p=0.019).

The prognostic factors associated with CUD in multivariate study and after adjusting confounding variables were more frequent manic relapses (p<0.001; ORa-18; IC95%3.9-88), subsyndromal symptoms (p=0.007; ORa-3.7; IC95% 1.4-9.8), more frequent hospitalizations (p<0.001; ORa-36; IC95% 4.3-310) and longer (p<0.001; ORa-5; IC95% 1.6-15.5), lack of socio-professional reintegration (p=0.001; ORa-5.3; IC95% 1.5-14.6) and overall malfunction (p=0.001; ORa 6.8; IC95% 2-22.6).

Association between socio-demographic characteristics related to type 1 bipolar disorder and cannabis use disorder: The single status in patients with BD1 was statistically associated with CUD (p=0.021). This result was consistent with the literature. Urban residence in patients with bipolar disorder was statistically associated with CUD (p=0.013). This could be explained by easier access to substances in urban areas. The literature on this subject remains limited [14]. Occupational instability, found in our study in patients with BD1 and CUD (p=0.001), has also been reported in the literature [15]. This could be explained by the functional disability secondary to the effect of *cannabis* on cognitive and executive functions and by the frequency of relapses of absenteeism [16]. Similarly, an alteration in intrafamilial relationships found in our study in patients with CUD (p-0.018) was demonstrated in a literature review and is linked to many socio-economic factors [17]. Also, we found that intrafamilial violence was statistically associated with CUD in our patients with bipolar disorder (p-0.04). This observation has also been found in the literature [18,19]. Indeed, CUD is more likely to develop violent behavior assessed at twice in the general population and 3.8 times in the psychiatric population [18].

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Association between clinical and therapeutic characteristics related to type 1 bipolar disorder and cannabis use disorder: A history of stay abroad was more found in our BD1 patients with CUD (p=0.008). These results are in line with those of the literature. This event could be a factor facilitating access to drugs, thus promoting the initiation or aggravation of addictive behaviors. A criminal history, with violence as a motive predominate, was more found in the CUD group (p=0.016). Our results were consistent with those in the literature that found that substance use disorder is a predictor of violent behavior in male patients with BD, estimated to be 2.8 times more likely to be violent [20]. This relationship could be explained by greater impulsiveness, facilitating the transition to aggressive action [21].

The problem of smoking was more common in patients with bipolar disorder CUD (p=0.042). This association has been explained by the fact that smoking in adolescence is considered an initiator to the abuse of other substances [22]. In addition, apart from the disjointed use of the two substances, the combination of *cannabis* and tobacco in artisanal cigarettes makes the use of *cannabis* most often inseparable from that of tobacco [23]. Occasional alcohol consumption was more found in the CUD group (p=0.001). Lev-Ran et al.[14], based on data from the National Epidemiological Survey of Alcohol and Related Conditions (NESARC) study [24], found that BD patients with *cannabis* abuse had nearly 6.5 times a risk of alcohol misuse than patients with BD who did not use the substance. This association between *cannabis* and alcohol has a negative impact on the evolutionary course of bipolar disorder with more suicide attempts, earlier onset of BD, higher frequency of depressive episodes, more psychotic characteristics, and general malfunction [25]. It was this negative impact of alcohol consumption on the evolutionary course of bipolar disease that led us to incorporate it into the multivariate study as a confounding variable. Personality disorders were more observed in our CUD population (p=0.008) particularly antisocial (p=0.003). Few works in the literature have been interested in the study of this association. In this sense, in the study of Lev Ran et al. [16], the authors found a prevalence of personality disorders in BD of 60.3% in the absence of *cannabis* and 80% in its presence. They also concluded, after adjusting for socio-demographic factors, that CUD increases the risk of having an antisocial personality disorder by 2.75 times [26]. For their chronologies of appearance, we found in our study that *cannabis* use chronologically preceded the onset of bipolar disease in 80% of BD1 patients. This finding has been reported in the literature and that substance abuse is thus a risk factor that precipitates and perpetuates thymic relapses [26,27]. The annual frequency of manic episodes was higher in our CUD patients (p<0.001). Our results join those of the literature with a risk of having new manic episodes is multiplied by 3 in cases of *cannabis* abuse according to the meta-analysis carried out by Gibbs et al. [28]. A poor insight has been more observed in our CUD patients (p <0.001) and in the literature [29] and is said to be related to a dysfunction of the neural circuits. Similarly, drug adherence and follow-up were worse in our CUD group (p=0.001). Indeed, in addition to the reported poor compliance in BD reaching up to 64% [30], a negative effect on compliance with treatment has also been linked to the CUD [31]. For treatment, long-acting antipsychotics were more commonly prescribed in the CUD group (p=0.007). The use of this form could be explained by poor adherence and poor insight associated with CUD [31].

Impact of cannabis use disorder on prognostic elements of type 1 bipolar disorder: In our study, CUD had a negative impact on the evolutionary course of BD1. The prognostic factors associated with CUD in multivariate study and after adjusting confounding variables were more frequent manic relapses (p<0.001; ORa-18; IC95% 3.9-88), subsyndromal symptoms (p<0.007; ORa-3.7; IC95% 1.4-9.8), more frequent hospitalizations (p<0.001; ORa-36; IC95% 4.3-310) and longer (p<0.001; ORa-5; IC95% 1.6-15.5), lack of socio-professional reintegration (p=0.001; ORa-5.3; IC95% 1.5-14.6) and overall malfunction (p=0.001; ORa 6.8; IC95% 2-22.6).

Indeed, the annual frequency of manic episodes, statistically associated with CUD in our study, persisted after controlling the confounding factors (p<0.001; ORa-18; IC95% 3.9-88). Our results are consistent with data from the literature with an annual frequency of thymic episodes of 1.8 in bipolar *cannabis* patients versus 0.7 in non-consumer bipolar patients.

For the quality of free intervals, the persistence of subsyndromic thymic symptoms statistically associated with CUD in our study, persisted after adjusting confounding variables (p=0.007; ORa-3.7; IC95% 1.4-9.8), thus joining the results found in the literature [15,32].

In addition, among the confounding factors, the persistence of subsyndromal thymic symptoms is confusing in the diagnosis of BD, which may thus be mistaken for a psychotic disorder or personality disorder. Indeed, a review of the literature by Singh *et al.* has shown that the factors that contribute the most to diagnostic errors in BD are substance use disorders and psychiatric comorbidities [7].

A higher frequency and a longer duration of hospitalizations persisted after adjusting confounding factors with respectively (p<0.001; ORa-36; IC95% 4.3-310) and (p<0.001; ORa-5; IC95% 1.6-15.5) [33]. The literature is not unanimous on this subject. For some authors, CUD increases the risk of recurrence of hospitalizations by 2.93 [34,35]. Others, who included patients with type 1 and type 2 BD [36], found no significant differences between consumer and non-consumer groups. This disparity between studies could be explained by methodological differences.

Socially and professionally, poor socio-professional integration, statistically associated with CUD in our study, persisted after controlling confounding factors (ORa-5.3; IC95%1.5-14.6). This has also been described in the literature. Indeed, the CUD also has a negative impact on socio-professional integration, increasing the probability of having this disability by 2.49 (OR-2.49; IC95% 1.16-5.39) with a dose-effective relationship between cannabis use and the degree of socio-professional disintegration [37]. Thus, substance abuse aggravates socio-professional disintegration by increasing absenteeism, medical complications, and iterative hospitalizations [38].

A marked impairment of overall functioning was found in BD1 patients with CUD after adjusting for confounding variables (ORa-6.8; IC95% 2-22.6). Our result is in line with those of literature. Indeed, a significant association between *cannabis* use and impaired functioning in patients with BD1 in various studies (p=0.013) and (ORa-1.81; IC95% 1.13-2.91).

Study Limitations

Today, addictive comorbidities are of great interest and are now a topical topic and a research trail. However, few studies have evaluated the impact of *cannabis* alone, among psychoactive substances, on the evolution of BD. Nationally, this is the first Tunisian study specifically focusing on the comorbidity between BD and CUD, which included only BD patients with CUD without other psychoactive substances and controlled confounding factors in multivariate analysis.

Nevertheless, our study has some limitations. Indeed, the sample size was significantly reduced. This was in line with the highly selective inclusion criteria including only CUD without other psychoactive substances for the population of BD1 patients who were consuming BD1 and especially since the study involved only one psychiatric department, hence some caution in the generalization of the results of the study. Similarly, the exclusive selection of patients followed for BD1 did not allow the results to be generalized to all BD, however, this choice allowed us to have a homogeneous study population. Also, the information collected regarding the CUD was based solely on patient-reported information and medical records and was not objectified by toxicology tests. This lack of objectivity may underestimate *cannabis* use.

Conclusion

Our study highlighted the deleterious impact of *cannabis* use disorder on the course and prognosis of bipolar disorder. Common in Tunisia and around the world, *cannabis* use disorder is a real scourge with negative consequences especially on mental health. Developing strategies for managing these comorbidities on a large scale and developing international consensus could be a research avenue and targets for curative and preventive action. As a result, strengthening psych educative measures, the broad involvement of social services, training primary care physicians in prevention through the use of standardized early identification tools, and training of psychiatrists in the management of these comorbidities could have a positive impact on mental health.

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