



CANNABIS USE AS A PREDICTOR OF EARLY ONSET OF BIPOLAR AFFECTIVE DISORDER

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ABSTRACT

Background: Age at onset (AAO) in affective disorders is of significant prognostic value. Substances like alcohol, cannabis may affect the onset, course and outcome of Bipolar Affective Disorder (BPAD). Cannabis, already has an established role as a risk factor for psychosis, specifically Schizophrenia. However, there is scarcity of research all over the world to assess its association with onset of BPAD, and none has been performed in India yet, which calls for the need of study in this regard.

Aim: To compare the age at onset of BPAD among subjects with prior history of cannabis use and those without cannabis use.

Methodology: An observational comparative study of individuals aged 18-45 years comprising two groups with BPAD based on presence or absence of cannabis use was done using purposive sampling technique. A proforma was administered with details pertaining to socio-demographic data, family and past history of psychiatric disorders, age at onset of cannabis use and first episode of mood disorder, frequency of cannabis use. Retrospective chart review using ICD-10 Criteria for the diagnosis of BPAD was done. Written informed consents were taken after institutional ethical committee clearance.

Results: Patients with Cannabis use prior to the onset of affective episode (Group 1) had a significantly earlier onset as compared to patients without prior cannabis use (Group 2). Mean age at onset of first affective episode among Group 1 was found to be 20.3 ± 3.74 while it was 23.5 ± 5.84 among Group 2 with a p-value of 0.0142 (*statistically significant*). Also, those with prior cannabis use had a longer duration of first affective episode.

Conclusion: We found clear differences among other clinical variables also in both the groups. In addition to earlier onset, the cannabis users tend to have longer duration of illness with poor adherence to medications, which can be attributed to continuous cannabis use after being diagnosed with mood disorder.

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INTRODUCTION

Age at onset holds significance in directing the diagnosis, and course in most of the psychiatric illnesses. It is of significant prognostic value in the course and outcome of affective disorders.¹ It varies from adolescence to mid adulthood. Other factors like history of affective disorders, psychotic disorder, personality disorders in family, male gender are some of the factors that are found to pose risk for early onset of bipolar affective disorder (BPAD).² Substances like alcohol, cannabis may also affect the onset, course and outcome of BPAD.

Cannabis, already has an established role as a risk factor for psychosis, specifically Schizophrenia. However, less research has been done to assess its association with affective disorders, BPAD in specific.

Some studies have been conducted in the same regard, suggesting that substance use may precede the onset of bipolar disorder, and can also be an end result following an affective episode.³ Cannabis is found to be the most illicit drug used among individuals with Bipolar affective disorder. Up to 38% of individuals with BPAD continue to use cannabis throughout life. However, the relationship between the age at onset of BPAD and use of cannabis preceding it is not well understood and focussed on in the previous studies.

Cannabis use prior to onset of affective disorders is viewed differently by different investigators. Some look at it etiologically, others as predisposing or precipitating and some as coexisting in an index case. Cannabis dependence has implications in management and has prognostic significance also. In view of many youngsters in India, using this illicit drug both recreationally and at abuse potential, it is important to investigate the association between its use and early onset of mental illness such as BPAD. The concept of 'brought forward time' in affective illnesses has been mentioned by many investigators and Cannabis is a potential culprit awaiting

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investigation. Many cultures have a soft corner for cannabis and many countries have legalised its use for palliative care and also for individual consumption. But the use of this substance is laced with controversy and we are still at the stand point of innocent until proven guilty! Moreover, there has been paucity of literature conducted in India in this regard, which calls for a need for this study.

Aims

To compare the age at onset and other clinical correlates of bipolar affective disorder among subjects with and without prior history of cannabis.

MATERIALS AND METHODS

It's an observational comparative study: case cohort study; subjects were selected by purposive sampling technique and were divided into two groups of 30 participants each, based on the presence or absence of cannabis use prior to the onset of their first affective episode. Patient charts were also used in some cases and cohorts to derive age at onset of BPAD.

The study was conducted from September 2018 to December 2018. Data collection was started after obtaining institutional ethical clearance. A written informed consent was obtained from each participant presenting to psychiatry in and outpatient department and diagnosed with Bipolar Affective Disorder according to ICD-10 criteria at the time of presentation. Subjects within the age group of 18-45 years, meeting ICD-10 criteria for Bipolar Affective Disorder, confirmed in the presence of one senior consultant, and one senior resident were included in the study. Subjects with history of substance use other than nicotine and cannabis, subjects with other co-morbid psychiatric disorders and those with severe medical co-morbidities requiring multiple hospitalizations were excluded from this study. Chart review was also done to get additional details regarding age at onset of BPAD and also prior history of Cannabis use. Variables measured in the study were as follows:

A family history of depression/bipolar disorder/schizophrenia or other psychotic disorders among first degree relatives was obtained. In this study, subjects with at least one first degree relative with one or more psychiatric disorder were considered to have a positive family history.

Age at onset of first affective episode was considered when the subject with BPAD (according to ICD-10 criteria), first met criteria for an affective (depressive/manic) episode.

Cannabis use assessment: Patients who reported use of cannabis (once/weekly/monthly/ meeting criteria for dependence as per ICD 10 criteria) prior to the onset of first affective episode were included under Group 1. While BPAD subjects without the use of cannabis, were included under Group 2.

Age at onset of substance use was considered as the age when the subject first started using cannabis.

STATISTICAL ANALYSIS

Statistical analysis were done using SPSS version 22, student independent t- test. Results were presented in the form of tables and pie charts.

RESULTS

Patients with Cannabis use prior to the onset of affective episode (Group 1) had a significantly earlier onset of BPAD as compared to patients without prior cannabis use (Group 2).

Table 1 Descriptive table: details regarding socio-demographic data

Variables	Group 1 (Cannabis use)	Group 2 (No cannabis use)	P-Value
Age(in years)			
Mean ± S.D	26.67 ± 5.98	30.90 ± 9.69	0.0465*
Sex			
Male	29	30	
Female	1	0	1.000 #
Religion			
Hindu	10	19	
Muslim	18	11	0.0392*
Christian	2	0	
Education			
Illiterate	0	1	
Primary school	2	0	
Middle school	4	0	
High school	9	15	
Pre-degree	9	11	
Degree	5	3	
Post Graduate	0	0	0.116 #
Professional degree/higher	1	0	

*statistically significant, # statistically not significant.

Table 2 Frequency of cannabis use prior to the first affective episode

Frequency of cannabis use	Number	Percentage (%)
Once	1	3.3
2-3	7	23.3
4-5	6	20.0
Cannabis dependence	16	53.3
Total	30	100.0

Mean age at onset of first affective episode among Group 1 was found to be 20.3 ± 3.74 while it was 23.5 ± 5.84 among Group 2 with a p-value of 0.0142 (statistically significant). (Table 3)

Table 3 Comparison of mean age at onset of first affective episode in Group 1 and Group 2.

GROUP	Age at onset of first affective episode (Mean ± S.D)	t-value	P-value
Group 1 (CANNABIS USE)	20.3 ± 3.74		
Group 2 (NO CANNABIS USE)	23.5 ± 5.84	2.5274	0.0142*

*statistically significant.

63.3% of cannabis users continued to use cannabis after being diagnosed with affective disorder. 83.3% of the subjects in Group 1 had mania as the first episode while 16.7% presented with depression (Diagram 1). Those with prior cannabis use had a longer duration of first affective episode with 33.3% remitting over 1 month, 53.3% over 2-3 months, while 13.3% over 3-6 months. In Group 2, in 66.7%, symptoms subsided over 1 month,33.3% over 2-3 months (Table 4).

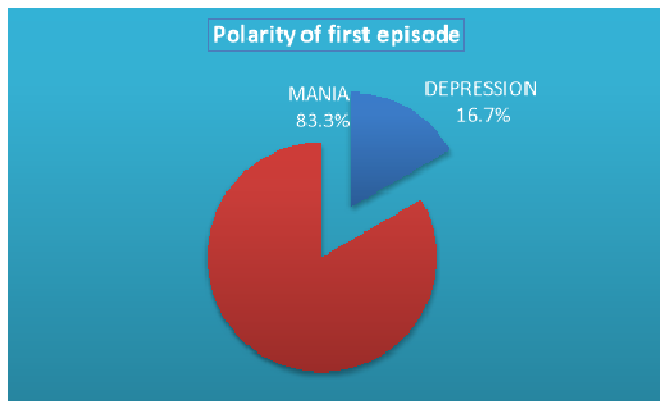


Diagram 1 Data regarding polarity of the index affective episode.

Among subjects with prior cannabis use, 19 (63.3%) continued to use cannabis even after the index episode (Diagram 2). Also, among cannabis users, we found a shorter inter-episodic length between the index episode and the second affective episode (1 ± 0.25 years) as compared to those without cannabis use (3.5 ± 1.25 years).

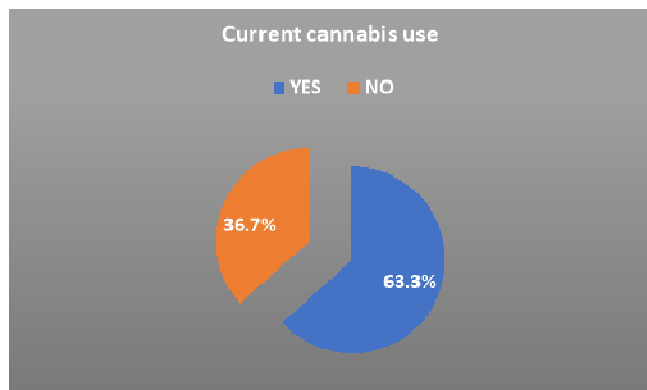


Diagram 2 Data regarding current cannabis use

Table 4 Data regarding duration of the index affective episode

Duration of first episode	Group 1 (CANNABIS USE)		Group 2 (NO CANNABIS USE)		P-Value
	Number	Percentage (%)	Number	Percentage (%)	
1 Month	10	33.3	20	66.7	0.013*
1-3	16	53.3	10	33.3	
3-6	4	13.3	0	0.0	
6-12	0	0.0	0	0.0	
>12	0	0.0	0	0.0	
Months	0	0.0	0	0.0	
Total	30	100.0	30	100.0	

*statistically significant.

Pre-morbid personality profile revealed 16.7% of cannabis users to have Cluster B traits, compared to 3.3% in Group 2; with a p-value of 0.069 (not significant). Three of the 30 subjects with prior cannabis use, while 4 out of 30 participants among the non-cannabis users had family history of mood disorder. The difference in the two groups w.r.t family history was not significant. 16 participants in Group 1, compared to 7 participants in Group 2 had history of poor drug compliance. The difference was statistically significant (p-value <0.05).

DISCUSSION

Previous studies by James⁴ and Taylor *et al*⁵ have emphasized that there is a high prevalence of substance use, mainly alcohol among patients who developed BPAD before the age of 30

years. Baethge *et al*³ found a strong association of cannabis use with manic or hypomanic episodes. Similar results are reported by Strakowski *et al*⁶ in a prospective study on cannabis users. The latter study however did not clarify on substance induced affective episodes as the primary assessment was done during hospitalization due to the first affective episode while the subjects were continuing cannabis use.

The current study is an attempt to understand the causal influences of cannabis on the onset of BPAD. A comparison of AAO and clinical correlates was done between two subgroups of subjects with BPAD, divided on the basis of use of cannabis prior to the index mood episode.

We discuss the results under two broad categories:

1. Age at onset across diagnostic sub-groups
2. A comparison of socio-demographics and clinical correlates between the two groups

Age at onset across diagnostic sub-groups

Patients with Cannabis use Patients with Cannabis use had significantly earlier onset (Group 1) as compared to patients without prior cannabis use (Group 2). Mean AAO of first affective episode in Group 1 was found to be 20.3 ± 3.74 while it was 23.5 ± 5.84 among Group 2 with a p-value of 0.0142 (statistically significant). Our findings were consistent with findings of studies by Lev-Ran *et al*⁷ and Lagerberg *et al*⁸, and a review article by Leite *et al*⁹ which reported of significant association of high frequency of cannabis use with AAO of affective disorder with a mean difference of 5 years, irrespective of the positive family history, other substance use.

This finding has significant clinical implication. Here the authors propose that the use of cannabis not only reduces the age of onset but also the 'well in between' interval. Educating vulnerable groups regarding same may have a bearing in delaying onset of BPAD. Late age at on set means fewer episodes, more opportunity for the individual to have finished education, secured employment and in India, a marital partner partner.

A comparison of socio-demographics and clinical correlates between the two groups

There was no statistically significant difference between the two groups in terms of age, gender and education status.

We found that a majority of subjects under Group 1 had manic episode as the index episode (83.3%). This was consistent with a previous study that suggests that people with cannabis use spend more time in mania than depression.¹⁰

We also found that prior cannabis use was associated with a longer course of first affective episode and a short cycle length between the index episode and the second affective episode. Also, these subjects showed poorer compliance to medications when compared to the subjects in the group without cannabis use. These findings conform to the findings from previous studies suggesting that use of cannabis and earlier onset of BPAD is associated with poorer outcome, increased episodic frequency, poor drug compliance and concurrent substance use.^{10,11,12} This finding is of importance when educating patient and families regarding management of an index case. Abstaining from Cannabis use may help to reduce days spent in an episode.

This study is one of the rare studies done in India with an objective to evaluate the relationship between preceding cannabis use and BPAD. A descriptive analysis of various clinical variables like cycle length, polarity of the index mood episode, drug compliance, current cannabis use adds to its merits.

The study centre is a tertiary care medical college postgraduate training institute. Charts are meticulously maintained for teaching purposes. The recall bias has been overcome to an extent due to availability of documentation in case charts. Also the diagnosis is strictly adhered to using the ICD-10 criteria.

We agree that one of the limitations of the study is its small sample size which is not representative of the general population, but sample size is statistically derived and in keeping with the frequency and confidence interval. However the findings warrant a future study with larger sample size.

There is a possibility of bias while recalling the details pertaining to the first affective episode in a retrospective manner. However, it was minimized by keeping the age criteria limited to 45 years. Also, another strength is, the possibility of substance induced psychotic disorders is ruled out by taking the subjects who met the diagnostic criteria for BPAD.

Our study has some additional interesting findings which need discussion. Pre-morbid personality profile of cannabis users revealed more Cluster B traits, compared to non users. This has to be viewed carefully as such individuals may default on treatment and continue to use substance and worsen treatment outcomes.

Family history of mood disorder was more prominent in the non user group revealed more Cluster B traits. These findings cannot be explained logically. Other mediating influences such as genetics need to be studied which are beyond the scope of this particular paper.

We humbly accept many limitations of our modest research. First and foremost there could be a sampling bias due to collection of data from hospital setting where certain patients may refuse consent or leave hospital prematurely. Also the study duration spanned only few months so it is not even a representation of a full years finding. Our sample size is small which further limits the generalisability of our results.

CONCLUSION

The main finding of our study was that cannabis use prior to onset of affective disorder is associated with an earlier age of onset of affective episode. Also users had more episodes at frequent intervals. These findings are in concurrence with the growing consensus that cannabis use is not only a risk factor for developing manic symptoms and Bipolar affective disorder, but is associated with poorer outcome by increasing the frequency of affective episodes.

Future directions: Eyes do not see what the brain does not know. Cannabis use we know, has a potential to precipitate psychosis. In our study we are implicating this universal favourite in the early onset of BPAD. However the study is small and the stakes are high. Before we label this illicit substance as causal and culprit, we need more evidence. This evidence has to come from larger sample size, larger studies, prospective ones spanning years to see it as it happens. There is a need for studies that simultaneously evaluate other

confounding factors which may influence AAO of affective disorders.

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Conflicts of Interest

None

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