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Cannabis use and related clinical variables in patients with obsessive-compulsive disorder

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37 **Abstract**

38 **Objective.** Limited studies have investigated cannabis use in patients with obsessive compulsive
39 disorder (OCD), despite its widespread use by patients with psychiatric illnesses. The aim of this
40 study was to assess the frequency, correlates, and clinical impact of cannabis use in an Italian
41 sample of patients with OCD.

42 **Methods.** Seventy consecutive OCD outpatients were recruited from a tertiary specialized clinic.
43 To assess cannabis-related variables, patients completed a questionnaire developed for the
44 purpose of this study, investigating cannabis use-related habits and the influence of cannabis use
45 on OCD symptoms and treatments. A set of clinician and self-reported questionnaires was
46 administered to measure disease severity. The sample was then divided into three subgroups
47 according to the pattern of cannabis use: "current users" (CUs), "past-users" (PUs), and "non-
48 users" (NUs).

49 **Results.** 42.8% of patients reported lifetime cannabis use and 14.3% reported current use. 10% of
50 cannabis users reported an improvement in OCD symptoms secondary to cannabis use, while
51 23.3% reported an exacerbation of anxiety symptoms. CUs showed specific unfavorable clinical
52 variables compared to PUs and NUs: a significant higher rate of lifetime use of tobacco, alcohol,
53 and other substances, and a higher rate of pre-OCD onset comorbidities. Conversely, the three
54 subgroups showed a similar severity of illness.

55 **Conclusion.** A considerable subgroup of patients with OCD showed a predisposition towards
56 cannabis use and was associated with some specific clinical characteristics, suggesting the need
57 for targeted consideration and interventions in this population.

58

59 **Keywords:** obsessive compulsive disorder; cannabis; substance use, prevalence, addiction.

60

61 **1. Introduction**

62 Obsessive compulsive disorder (OCD) is a prevalent and highly disabling psychiatric illness
63 responsible for a substantial reduction in quality of life and a significant functional impairment for
64 patients and their caregivers ¹⁻³.

65 Available treatments for OCD are at times only partially successful and treatment resistance might
66 be a reason for patients' drop-outs with conventional medications ⁴. In some circumstances,
67 patients might use alternative substances to self-medicate or to cope with OCD symptoms. Among
68 these, cannabis is the most widely used substance of abuse in the United States among youths
69 and adolescents, due to its easy availability and affordable price. In a general population survey
70 conducted in the USA, one-year prevalence of cannabis use amounted to 34.5% of adults between
71 18 and 25 years old ⁵. In a cross-national study, the prevalence of cannabis use disorder in Italian
72 adolescents reached 2.77%, with a slightly higher rate in males than females (3.49% vs 2.09%) ⁶.
73 Considering patients with OCD typically manifest the first symptoms during the school age ⁷, these
74 data might suggest an overlap of OCD and cannabis use in terms of age distribution, with young
75 subjects being the most affected in both disorders.

76 Conventionally, impulsivity is the most important dimension involved in substance use disorders ⁸.
77 However, compulsivity has been recently proposed as a determinant to addiction ⁹, being a
78 common feature of OCD, as suggested by neurological and neuropsychological mechanisms
79 coexisting in these disorders ^{10,11}. On the other hand, several studies exploring brain models of
80 addiction and risk-oriented behaviours underlined the presence of high impulsivity in OCD patients
81 ¹²⁻¹⁴. This characteristic is somehow opposite to personality traits characterized by harm-avoidance
82 typically expressed by patients with OCD ¹⁵⁻¹⁷ which, in turn, might discourage OCD patients from
83 involving themselves in potentially dangerous and unsafe situations often connected to substance
84 use. Overall, substance use in OCD might be considered a result of a complex overlay and
85 interplay of compulsivity, impulsivity, personality traits, and likely other dimensions whose roles
86 need to be further investigated.

87 Previous investigations sought to describe the correlation between cannabis use and OCD. The
88 first, evidence from both animal and human studies suggests that the endocannabinoid system
89 may play a role in OCD and related disorders ¹⁸. A recent study, based on data from an online
90 survey, assessed patterns of cannabis use in a large sample of individuals with a diagnosis of
91 OCD (N=601, based on a self-reported prior diagnosis by a healthcare profession or well-
92 established cutoff on the OCI-R) ¹⁹. 42% of participants with OCD met cannabis use disorder
93 criteria and nearly 70% for problematic cannabis use. Among negative factors associated with
94 cannabis use, most participants were not currently receiving evidence-based OCD treatment, and
95 the likelihood of this treatment decreased as cannabis use frequency increased.

96 Deepening the correlation between cannabis and OCD, some investigations reported cannabis use
97 as a potential harmful factor for OCD. One study that primarily investigated prevalence, correlates,
98 and predictors of OCD in a large (N=390) birth cohort showed that a history of substance use
99 disorder (cannabis/alcohol) was a prospective risk factor for OCD ²⁰. Challenging this finding, a
100 prospective study in an adult population, recruited through a national survey, showed that cannabis
101 use at baseline was unrelated with an increased risk of OCD diagnosis within 3 years of follow-up
102 ²¹. On the other hand, some investigations collecting cannabis users reported how OC symptoms
103 severity predicted more frequent cannabis use ^{22,23}.

104 Furthermore, the effect of cannabis on OC symptoms has been investigated in some studies. Thus
105 far, there have been only two small cannabinoid trials in individuals with OCD. With the limitation of
106 a small sample (12 patients with OCD), a placebo-controlled investigation of different
107 concentrations of tetrahydrocannabinol and cannabidiol suggested that smoked cannabis has little
108 acute impact on OC symptoms, compared to placebo ²⁴. In the second trial, 11 patients received
109 nabilone over four weeks showing little effect on OC symptoms ²⁵. Conversely, the recent online
110 survey from Kayser and colleague reported a relevant amount of participants (68.3%) experienced
111 cannabis typically improved their obsessions to varying degrees, while a subset reported that
112 cannabis worsened obsessions (17.3%) or compulsions (13.8%) ¹⁹. Another study including 87
113 individuals self-identifying with OCD, measured (as tracked with a mobile app) a 60% reduction in
114 compulsions and a 49% reduction in intrusions from before to after inhaling medical cannabis ²⁶.

115 Other evidence of the effect of cannabis on OC symptoms is based on case reports, which showed
116 a variable degree of improving after receiving dronabinol, a synthetic oral form of THC ^{27,28} or
117 medicinal cannabis treatment ²⁹.

118 Although the results of this sparse literature suggest a possible link between OCD and cannabis
119 use, to the best of our knowledge only limited studies have primarily investigated cannabis use in
120 patients with OCD. In addition, the favoring role of specific socio-demographic or clinical features in
121 cannabis users has not been investigated. Therefore, the primary aim of this study was to
122 describe, in an Italian sample of patients with OCD, the frequency, correlates, and predictors of
123 cannabis use and its impact on OC symptoms and on prescribed medications. Additionally, we
124 wanted to stratify the sample according to the degree of cannabis use. We hypothesized that
125 patients with sustained cannabis use would manifest more unfavorable sociodemographic and
126 clinical characteristics compared with patients with discontinuous use or who never use this
127 substance. This work is part of an international multicenter study in collaboration with the
128 Department of Psychiatry and Behavioral Neuroscience at McMaster University in Canada and the
129 present report illustrates the preliminary results of the Italian sample.

130

131

132 **2. Methods**

133 **2.1 Participants**

134 This retrospective and observational study was conducted at “Luigi Sacco” University Hospital in
135 Milan, Italy. Patients with OCD were recruited from a tertiary psychiatric service dedicated to the
136 diagnosis and treatment of outpatients with OCD. Recruitment took place between May 2019 and
137 September 2021.

138 Inclusion criteria were: adult subjects (over age 18 years) with a diagnosis of OCD confirmed by
139 trained psychiatrists through the administration of the Structured Clinical Interviews for DSM-5
140 (SCID), clinical version ³⁰. In case of psychiatric comorbidities, OCD had to be considered the
141 primary disorder and directly responsible for OC symptoms. Exclusion criteria included brain
142 diseases, intellectual disability, and psychiatric disorders secondary to a medical condition.

143 The study was conducted in accordance with the declaration of Helsinki ³¹. Patients provided their
144 written informed consent to participate in this study and to use their anonymized data for research
145 purposes.

146

147 **2.2 Measures**

148 All patients were screened using a specific questionnaire developed for the purpose of the study,
149 which was edited by the McMaster University Anxiety Working Group (through a collaboration of
150 the International College of Obsessive-Compulsive Spectrum Disorders (ICOCS)). This
151 questionnaire specifically investigated the frequency and related features of cannabis use in a
152 clinical population of patients with OCD (see Supplementary material for the extended version).

153 The questionnaire comprises 34 questions administered at baseline by specifically trained
154 research investigators. The first part of the questionnaire collected sociodemographic variables,
155 including gender, age relationship status, ethnicity, living situation, highest level of education
156 achieved, and occupational status. The second section focused on current and previous
157 treatments for OCD (including psychotropic medications and psychotherapeutic approaches)
158 assessing the perceived effectiveness and the reasons for discontinuation of previous treatments.

159 The third section of the questionnaire investigated current and past use of any substance of abuse.
160 Additional questions focused on cannabis use-related habits. In particular, the following information
161 was collected: type of cannabis used (dried leaves or flowers, oils, edible, tinctures), frequency of
162 use in the past week, average amount of cannabis consumed during a typical use and amount of
163 cannabis consumed daily. Additionally, patients were asked to report if they were prescribed
164 cannabis to treat OCD symptoms or another medical condition. The last questions focused on the
165 influence of cannabis use on OCD symptoms (e.g., improving or worsening OCD symptomatology
166 after cannabis use) and on OCD treatments (e.g., use of cannabis to treat OCD symptoms instead
167 of a prescribed medication/psychotherapy).

168 Additionally, to assess patients' clinical picture at study entry, the questionnaire comprises three
169 validated self-reported questionnaires: the Obsessive-Compulsive Inventory-Revised to measure
170 obsessive-compulsive traits (OCI-R) ³², the 9-item Patient Health Questionnaire to measure

171 depressive symptoms (PHQ-9) ³³, and the Generalized Anxiety Disorder-7 scale to assess
172 symptoms of general anxiety (GAD-7) ³⁴.

173 Patients' medical records were analyzed to integrate additional clinical variables, in particular age
174 at illness onset (AAO), age at first treatment, duration of untreated illness (DUI, defined as the time
175 interval – in months – elapsing between the onset of the disorder and the administration of the first
176 adequate psycho-pharmacological treatment), psychiatric comorbidities (pre-existing or occurring
177 after the onset of OCD), and family history of psychiatric disorders. OCD symptoms severity was
178 assessed at study entry by trained clinicians also through the administration of the Yale-Brown
179 Obsessive-Compulsive Rating Scale (Y-BOCS) ³⁵.

180

181 **2.4 Statistical analysis**

182 Descriptive analyses of socio-demographic and clinical variables were performed for the whole
183 sample. Additionally, descriptive analyses of habits related to cannabis use were performed in the
184 subgroup of patients who reported current or lifetime cannabis use.

185 To stratify the sample according to the degree of cannabis use, we adopted the following criteria,
186 which were previously adopted in an ICOCS study investigating cigarette smoking in OCD Patients
187 ³⁶: “current users” (CUs), i.e., patients who used cannabis within 6 months prior to study entry;
188 “past users” (PUs), i.e., patients who used cannabis in their lifetime but discontinued at least 6
189 months before receiving the questionnaire; and “non-users” (NUs), i.e., patients who had never
190 used cannabis in their lifetime. This distribution ideally reflected different severities of cannabis use
191 in terms of frequency and duration, where CUs were patients with a more sustained and severe
192 form of substance use, compared with PUs that used cannabis in their past, and, lastly, compared
193 with NUs who ideally did not share risk factors for cannabis use.

194 Non-parametric Kruskal-Wallis and chi-squared tests were used to compare the three subgroups
195 with respect to continuous and categorical variables. Statistical significance was set at $p < 0.05$.
196 Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS)
197 version 26 software (IBM Corp.; Armonk, NY, USA).

198

199 3. Results

200 3.1 Sample description

201 Seventy consecutive patients were included in the study (females: 57%, mean age: 37.1±13.4
202 years). Nearly all patients were identified as Caucasian (98%). Table 1 outlines the main socio-
203 demographic and clinical features of participants.

204

205 *Table 1 about here.*

206

207 The mean age at onset was 21.1 (±10.6) years, and 42.9% of patients had an onset before 18
208 years of age. The mean age at first treatment was 25.7 (±10.4) years and the mean DUI was 58.9
209 (±81.4) months. The Y-BOCS showed a mean score of 21.5±9.5, the OCI-R of 23.8±12.6, the
210 PHQ-9 of 11±6., and the GAD-7 of 9.7±5.4.

211 Nearly all patients (91.4%) were prescribed a specific pharmacological treatment for OCD, while
212 few of them had never assumed treatment or had stopped treatment before study entry. Most of
213 the sample was prescribed antidepressant medications (90%), more than one out of four
214 antipsychotics (28.5%), one out of ten mood stabilizers (7.1%). 17.1% of patients were currently
215 receiving psychotherapeutic treatment. The perceived satisfaction about the efficacy of the
216 treatments for OCD was 6.5±2.6 on a scale from 0 (extremely dissatisfied) to 10 (extremely
217 satisfied). However, more than half of patients reported they had suspended or changed a previous
218 treatment for OCD because of lack of efficacy (54.3%) or adverse drug reactions (24.3%).

219

220 3.2 Habits related to cannabis and other substances use

221 With respect to cannabis use, 40 subjects had never used cannabis in their life (NUs, 57.1%),
222 while 30 patients (42.9%) had. Among those who had used cannabis, 20 subjects had not used
223 cannabis six months prior to study entry (PUs, 28.6% of the total sample), while 10 patients (CUs,
224 14.3% of the total sample) were still using it.

225 With respect to other substances, 50% of patients reported a lifetime use of tobacco, 67.7%
226 reported a lifetime use of alcohol, 40.8% a combination of cannabis and alcohol use, and 7.2%

227 used other substances. Moreover, 19.9% of patients reported having used, in their lifetime,
228 prescription medications (i.e., painkillers, anxiolytics, sleep aids/sedatives, stimulants outside the
229 therapeutic regimen, on higher doses or frequency). In the last 6 months, 37.1% of patients
230 reported tobacco use, 58.5% alcohol, 12.8% a combination of cannabis and alcohol, and 10%
231 prescription medications.

232 Among CUs, only one patient reported a cannabis consumption in the week prior to study entry. In
233 a typical session, all subjects reported using 0.25g or less of cannabis and using dried flower/leaf
234 (smoked or vaporized) or oils.

235 Focusing on the effect of substances use on OC symptoms, 30% the total sample reported to have
236 consumed a substance with the purpose to treat or help managing OC symptoms. In particular,
237 cannabis was used for this purpose in 10% of patients, alcohol in 15.7%, tobacco in 7.1%, and
238 prescription psychotropic drugs in 8.5%. Among cannabis users, a minority (10%) reported that this
239 substance had helped reducing OC symptoms, with an average satisfaction score of 1.4 ± 2.9 on a
240 scale from 0 (not at all effective) to 10 (extremely effective). Further details on the impact of
241 cannabis on OC symptoms revealed that one patient (3.3%) reported a reduction in the number of
242 intrusive thoughts, one (3.3%) a cessation of obsessions, and one (3.3%) a decrease in general
243 anxiety. On the other hand, 23.3% of cannabis users reported a worsening of OC symptoms
244 because of their cannabis use, associated with an increase in general anxiety.

245 No patient reported to have used cannabis instead of their prescribed treatment for OCD.
246 Additionally, no patient reported to have reduced their prescribed OCD medications dose because
247 of cannabis use or went off of OCD treatment or chose to use only cannabis to treat their OC
248 symptoms. Only one patient (1.4%) reported using a cannabis prescription for a different medical
249 condition (i.e., chronic pain) than OCD.

250

251 **3.3 Comparison between current cannabis users, previous users, and non-users**

252 Figures 1 and 2 outline significant differences between the three subgroups.

253

254 *Figure 1 and Figure 2 about here.*

255

256 PUs and CUs showed a lower age (31 ± 10.6 and 31.4 ± 11.3 years, respectively) compared to NUs
257 (41.4 ± 14.5 , $p=0.01$). No significant differences emerged between the three subgroups with
258 respect to gender, living situation, highest level of education achieved, employment, or relationship
259 status.

260 Considering clinical variables, age at first treatment was significantly earlier for PUs and CUs
261 (20.9 ± 5.2 years and 22.4 ± 5.3 years, respectively) compared to NUs (29.2 ± 12.2 years, $p=0.033$).

262 Considering disease severity, CUs showed a slightly higher Y-BOCS total score (24.3 ± 7.3)
263 compared to PUs (19.9 ± 8) and NUs (17.6 ± 10.1), but not at a statistically significant level. On self-
264 reported questionnaires, NUs showed a lower mean score on the PHQ-9 and on the GAD-7 scale
265 compared to PUs and CUs (PHQ-9: NUs: 10.6 ± 6.5 , PUs: 11.2 ± 5 , CUs: 12.2 ± 6.2 ; GAD-7:
266 NUs: 8.9 ± 5.8 ; PUs: 11.2 ± 4.9 ; CUs: 10.1 ± 3.9) and on the OCI-R compared to PUs (NUs: 22.6 ± 11.7 ;
267 PUs: 27.3 ± 15.1 ; CUs 21.2 ± 9.9), although these differences were not significant.

268 With respect to comorbidities, a pre-OCD onset comorbidity was significantly more common in CUs
269 (90%) compared to NUs (55%) and PUs (60%, $p=0.033$). In detail, pre-OCD onset bipolar disorder
270 II was significantly more frequent in CUs (20%) compared to PUs (0%) and NUs (2.5%, $p=0.027$).

271 The prevalence of post-OCD onset comorbid major depression emerged to be higher among NUs
272 (32.5%) versus the other subgroups (PUs: 0% and CUs: 20%, $p=0.015$); post-OCD onset
273 comorbidity with any psychiatry disorders did not differ significantly among the three subgroups.

274 Considering current medications, NUs were treated more frequently with more than two
275 psychotropic drugs (25%) compared to PUs and CUs (5% and 0%, respectively, $p=0.045$).

276 Additionally, compared with NUs, PUs and CUs showed a more frequent use of substances other
277 than cannabis. In particular, lifetime alcohol use emerged to be significantly more frequent in PUs
278 (100%) and CUs (90%) than NUs (45%, $p<0.001$) and this difference was confirmed when the
279 question referred to the past 6 months, although not at a significant level (PUs: 75.0%, CUs: 90%,
280 NUs: 67.5%). Moreover, PUs (35%) and CUs (50%) reported to have consumed more frequently
281 more than one alcoholic drink daily compared to NUs in the past 6 months (10%, $p=0.034$).

282 Considering the use of alcohol as a coping strategy for OC symptoms, PUs and CUs (25% and

283 40%, respectively) reported the use of alcohol as self-medication more frequently than NUs (5%,
284 $p=0.01$). With respect to tobacco use, similar results emerged. Lifetime tobacco use was
285 significantly more frequent in PUs (75%) and CUs (70%) than NUs (32.5%, $p=0.003$); the same
286 difference emerged also for the previous six months (CUs: 70% vs PUs: 50% vs NUs: 22.5%,
287 $p<0.001$). Lifetime use of at least one other substances of abuse (i.e., cocaine,
288 amphetamine/methamphetamine, inhalants, hallucinogens, or heroin) was significantly higher in
289 CUs (100.0%) and PUs (100%) compared to NUs (70%, $p=0.004$).

290

291 **4. Discussion**

292 In the present sample, 42.8% of patients with OCD reported lifetime cannabis use (PUs plus CUs).
293 This percentage is understandably higher compared to a previous general population survey that
294 indicated 1-year cannabis use in 34.5% of young adults ⁵, being likely related to the different
295 periods of time that were investigated (lifetime vs 1 year, respectively). Among patients who had
296 used cannabis, 14.2% reported cannabis use in the six months prior to study entry (CUs),
297 reflecting more sustained and habitual use. Our results seem to underestimate the use of cannabis
298 in OCD patients if comparing to the recent study from Kayser and colleagues, where nearly 90% of
299 participants reported using cannabis at least one day over the previous month and nearly 60%
300 reported using cannabis at least daily ¹⁹. This latter study was conducted in the USA which shows
301 an increasing access to cannabis both for recreational and therapeutic uses compared to
302 European countries, and, additionally, the data could have been biased since only participants with
303 at least one lifetime use of cannabis were recruited in the survey.

304 With respect to other substances, a considerable number of patients investigated in the present
305 study reported lifetime use of tobacco and alcohol (50% and 67.1%, respectively). Comparing our
306 findings with previous studies (reporting rates ranging between 7% and 22.4% ^{37,38}), we found an
307 overall higher rate of smoking habits (50%). Cigarette smoking in OCD outpatients has been
308 studied in a previous report from the ICOCS, showing a cross-sectional prevalence of 24.4% in the
309 sample, and tobacco smokers were more frequently associated with comorbidity with Tourette'
310 syndrome and tic disorder and with a higher number of suicide attempts ³⁶. A recent systematic

311 review, aimed at assessing the therapeutic use of nicotine on OC symptoms, showed some
312 efficacy in treatment-refractory OCD patients ³⁹. Therefore, tobacco might be potentially used by
313 more severe patients as a self-medication strategy. The prevalence of alcohol use disorder in OCD
314 differs among recent studies (rates ranging from 7.5% to 20%) ^{40–42} and has been associated with
315 compulsivity trait ⁴³, male gender, and an increased risk of suicide ⁴¹. Additionally, in our sample
316 around two out of ten patients reported lifetime use of other non-prescription medications (19.9%)
317 and other substances of abuse (7.2%). These data seem to support a certain predisposition
318 towards substance use in OCD patients. This phenomenon has been investigated and debated in
319 the literature, with controversies about its reasons and frequency ⁴⁴. On one hand, OCD is
320 phenomenologically characterized by compulsivity and impulsivity ¹² that would drive affected
321 individuals to use substances while, on the other hand, OCD patients often show a harm-
322 avoidance phenotype, which would elicit the opposite effect. The prevalence of a full-blown
323 substance use disorder varied extensively in previous literature investigations, from 1% (in an
324 international multicenter study carried out on community samples of patients with OCD ⁴⁵) to 11%
325 (in a large Danish population study ⁴⁶). These differences are probably related to different sampling
326 procedures. In a cross sectional population survey conducted in the Netherlands, the life-time and
327 12-month odds of being diagnosed with a substance use disorder in subjects with OCD was
328 significantly higher than the odds for people without a psychiatric disorder and, in men, the co-
329 occurrence of substance dependence and OCD was significantly higher than the co-occurrence of
330 substance dependence and any other psychiatric disorders ⁴⁷. On the contrary, the hypothesis that
331 OCD and substance use are not related emerged in some studies showing that both alcohol and
332 drug misuse disorders were not significantly associated with OCD ⁴⁸. In another report, moreover,
333 substance use disorder was half as common in OCD patients than in the general population ⁴⁹.
334 These mixed results underline the need to further investigate the reasons behind substance use in
335 OCD which may be related to different comorbidity profiles and trajectories of OCD course.
336 In this light, the present study showed that 30% of OCD patients used a substance of potential
337 abuse during their lifetime to treat or to help manage their symptoms. In particular, alcohol was the
338 most used substance for this purpose (15.7%), followed by cannabis (10%), other prescription

339 medications (8.5%), and tobacco (7.1%)). A minority of cannabis users (10%) reported that this
340 substance has helped treat OCD symptoms (in reducing the number of obsessions or levels of
341 general anxiety), even if they considered this effect minimal (average level of satisfaction around 2
342 on a scale from 0 to 10). Interestingly, no improvements in compulsions were reported. On the
343 other hand, 23.3% of cannabis users reported a worsening of OCD symptoms because of
344 cannabis use (i.e., increase of general anxiety). Even though the limited sample size did not allow
345 us to discover if an effect was more frequent than the other, we could state these effects were not
346 univocal among patients. In the Italian culture, cannabis is often used as an illicit substance outside
347 of government authority's control, although the recent legalization of medical cannabis has not, so
348 far, lead to cannabis being indicated as a treatment for anxiety disorders. Consequently, it is not
349 surprising that the effects of cannabis use were different, presumably also reflecting the variability
350 of concentration of phytocannabinoids, the different administrations, the amount of substance
351 consumed on one occasion, and the frequency and total period of use ⁵⁰. Indeed, OCD patients
352 might decide to experiment with cannabis due to the partial efficacy of conventional medications (in
353 our sample treatment satisfaction was around 6.5 on a scale from 1 to 10). However, we observed
354 that no patient used cannabis to reduce or stop the therapy already prescribed by their treating
355 psychiatrist. Nonetheless, the social perception related to the effect of cannabis might have led to
356 the cannabis use as a coping strategy to handle anxiety or OC symptoms. Relaxation and tension
357 reduction were the most commonly reported effects of cannabis use in previous investigations that
358 demonstrated a positive effect of cannabis use for anxiety ^{51,52} and other psychopathological
359 dimensions (i.e., to cope) ⁵³⁻⁵⁵.

360

361 Considering the second aim of the present study, our hypothesis that patients who used cannabis
362 were clinically more severe was supported by the higher frequency of more severe clinical
363 variables in cannabis users. First, CUs and PUs showed a younger mean age and an earlier mean
364 age of first treatment than NUs. As reported in the literature, younger subjects are the ones more
365 frequently using cannabis and presumably, CUs and PUs received earlier clinical attention or
366 showed an earlier full-blown expression of the disease due to a higher illness severity.

367 Another variable associated with a higher disease severity was the presence of psychiatric
368 comorbidities. CUs showed an additional psychiatric comorbidity before and after the onset of
369 OCD, although only pre-onset comorbidity rate was significantly higher in this subgroup compared
370 to PUs and Nus. Additionally, CUs showed a significantly higher rate of pre-OCD onset comorbidity
371 with bipolar disorder II, compared with NUs and PUs.

372 The comorbidity between OCD and bipolar disorder has been extensively investigated. In a recent
373 meta-analysis, 13.5% of patients with OCD had a comorbid bipolar disorder, with more severe
374 OCD symptoms during depressive episodes and decreased severity during manic or hypomanic
375 episodes ⁵⁶. An international multicenter study conducted by the ICOCS reported that a higher
376 number of hospitalizations, more frequent add-on therapy, and a higher severity of OCD symptoms
377 were observed in the cases of comorbidity with bipolar disorder ⁵⁷. This is likely the case of the
378 CUs subgroup investigated in the present study, reflecting a higher severity of the disease.

379 Conversely, a significantly higher rate of comorbidity with major depression disorder emerged in
380 NUs compared to CUs and PUs. Indeed, depression is such a common comorbidity that it does not
381 need cannabis use to manifest itself. However, this finding needs to be further examined, and a
382 large sample seems necessary to better understand the impact of this comorbidity.

383

384 Other clinical variables that have been consistently associated with greater disease severity in
385 different psychiatric disorders including OCD ⁷ emerged to be more frequent in CUs compared to
386 the other subgroups. In detail, CUs showed a longer DUI and an earlier AAO compared to the
387 other subgroups. Despite the earlier age of first treatment, CUs showed a longer DUI (more than 6
388 years) compared with NUs (5 years) and PUs (less than 4 years). Considering available literature
389 on OCD, the DUI is high (up to around 10 years in adults) and a longer DUI has been correlated
390 with poor treatment response and with considerable suffering for the individual and their families ⁵⁸⁻
391 ⁶⁰. The reasons why patients who use cannabis have a longer DUI has not been investigated in
392 patients with OCD thus far. Previous studies reported how cannabis use ^{61,62} and substance use
393 disorder ⁶³ were responsible for a longer duration of untreated psychosis. In the present sample,
394 we might cautiously suggest that the same effects took place in the context of DUI in patients with

395 OCD. Moreover, CUs showed an average AAO younger than 18 years ((AAO around 16.3 years),
396 and this has been identified by some authors as the “early onset” OCD phenotype, previously
397 associated with male gender, a longer DUI ⁶⁴, a more frequent family history for OCD, as well as
398 comorbidity with tic disorders ⁶⁵.

399 Similarly, psychometric questionnaires revealed a greater degree of OC, depressive, and general
400 anxiety symptoms in CUs and PUs, compared to NUs. All these differences presumably reflect a
401 higher disease burden in patients with cannabis use, although not reaching a statistically significant
402 difference; a wider sample size might increase the statistical significance.

403

404 Outside cannabis use, CUs and PUs showed a higher tendency to other substances consumption,
405 as highlighted by a significantly more frequent lifetime use of alcohol, cigarette smoking, and illicit
406 substances compared with NUs. This association was maintained even in the closest temporal
407 range, with alcohol and tobacco (the latter at a statistically significant level) more frequently used in
408 PUs and CUs than NUs in the six months prior to study entry. The higher use of alcohol, cigarettes,
409 and other substances might be a consequence of a substance-use diathesis manifested by
410 cannabis users. On the other hand, it might reflect another effort to cope with OC symptoms (i.e.,
411 alcohol use to reduce anxiety derived from obsessive thoughts) not adequately treated with
412 conventional medications. Indeed, NUs showed to be more frequently on polypharmacotherapy,
413 compared to CUs and PUs, which might reflect a better care of these patients, with consequently
414 better response to their OC symptoms and therefore a lower tendency to reach for other
415 substances to manage their OC symptoms.

416

417 Some limitations should be considered in the interpretation of results. First, our data showed
418 cannabis users being the ones associated with more severe markers of illness with respect to
419 OCD, however this relationship might have been influenced by other variables (e.g., a greater
420 number of comorbid conditions), not being primarily related to cannabis use. Considering that
421 cannabis is perceived as an illegal substance in Italy, patients might have been fearful of disclosing
422 their use of cannabis to study investigators or have minimized how much of this substance that

423 they used. Moreover, the cross-sectional/retrospective collection of data may have influenced the
424 results, with longitudinal data being likely more informative. Additionally, lifetime/current cannabis
425 or other substances use were the only variables related to substance use that have been collected.
426 Indeed, other characteristics related to substance use disorders (i.e., impaired control, social
427 impairment, risky use, and pharmacological implications derived from substances) were not
428 investigated and deserve further study. Lastly, the limited sample size did not allow us to perform
429 additional subgroups analyses that would have better described the impact of specific variables.

430

431 **5. Conclusion**

432 Overall, the specific pattern of substance use might contribute to the identification of a specific
433 subgroup of patients with OCD that manifest a low level of harm-avoidance trait and more
434 consistent impulsivity traits (although not measured in this study). Further specific investigations
435 targeted to explore the impact of neuropsychological traits will need to be evaluated in future
436 studies. Additionally, considering that these features might be associated with more severe clinical
437 variables, clinicians should pay specific attention to substance use during the assessment in order
438 to correctly identify and address these patients using specific therapeutic approaches. Considering
439 the young age and the brain susceptibility of these patients, we believe additional attention must be
440 raised at clinical and at societal levels. Lastly, potential interference of cannabis with
441 pharmacokinetics of OCD medications is another area of potential concern that require further
442 evaluation.

443

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452

453 **Disclosures.**

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463

464 **Ethics Statement.** The study was conducted in accordance with the declaration of Helsinki. The
465 patients provided their written informed consent to participate in this study and for the use of their
466 anonymised data for research purposes.

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671 **Table**672 **Table 1.** Sociodemographic and clinical variables of the whole sample and in the three subgroups.

Variables	All patients	NUs	PUs	CUs
Number (%)	70 (100)	40 (57.1)	20 (28.6)	10 (14.3)
Age (years, mean \pm SD)	37.01 \pm 13.8	41.4 \pm 14.5	31 \pm 10.6	31.4 \pm 11.3
Female gender (%)	57.1	55	55	83.3
Education (%)				
Secondary school	14.3	7.5	25	20
High school	54.3	55	55	50
University	31.4	37.5	20	30
Employment (%)				
Unemployed	24.5	27.5	20	20
Employed	55.7	55	65	40
Student	20	17.5	15	40
Co-habitation (%)				
Alone	15.7	17.5	15	10
Family	42.9	40	50	40
Family of origin	40	42.5	35	50
In a stable relationship (%)	52.9	45	65	60
Age of onset (years)	21.1 \pm 10.6	24.1 \pm 12.2	17.7 \pm 5.8	16.3 \pm 7.9
< 18 years (%)	42.9	37.5	40	70
Age at first treatment (years)	25.7 \pm 10.4	29.2 \pm 12.2	20.9 \pm 5.2	22.4 \pm 5.3
DUI (months)	58.8 \pm 81.4	61.9 \pm 89.7	43.8 \pm 75.6	77.3 \pm 57
Y-BOCS	21.5 \pm 9.5	17.6 \pm 10.1	19.9 \pm 8	24.3 \pm 7.3
OCI-R	23.8 \pm 12.6	22.6 \pm 11.7	27.3 \pm 15.1	21.2 \pm 9.9
PHQ-9	11 \pm 6	10.6 \pm 6.5	11.2 \pm 5	12.2 \pm 6.2
GAD-7	9.7 \pm 5.4	8.9 \pm 5.8	11.2 \pm 4.9	10.1 \pm 3.9
Family history of psychiatric disorder (%)	64.3	57.5	75	70
Psychiatric comorbidities (%)				
Pre-onset (any)	65.7	55	60	90
Bipolar Disorder II	4.3	2.5	0	20
Post-onset (any)	65.7	70	55	70
Major Depression	21.4	32.5	0	20
Tourette Syndrome	8.6	2.5	15	20
Current medication (%)				
Antidepressants	90	90	95	80
Antipsychotics	28.5	37.5	15	20
Mood stabilizers	7.1	7.5	5	10
Psychotherapy	17.1	12.5	25	20
Polytherapy (> 2 drugs)	15.7	25	5	0
Substance use lifetime (%)				
Cannabis	42.9	0	100	100
Tobacco	50	32.5	75	70
Alcohol	67.1	45	100	90
Other substances	82.8	70	100	100
Non-prescription medications	19.9	22.5	10	30
Substance use past six-months (%)				
Cannabis	14.2	0	0	100
Tobacco	37.1	22.5	50	70
Alcohol	51	67.5	75	90
> 1 alcoholic drink daily (%)	22.8	10	35	50
Substance use to cope with OC symptoms (%)				
Cannabis	14.2	0	0	100
Alcohol	15.7	5	25	40

673

674 **Legend:** CUs: current cannabis users; NUs: non cannabis users, PUs: past cannabis users; DUI: duration of untreated illness; GAD-7:
675 General Anxiety Disorders Scale; OCI-R: Obsessive-Compulsive Inventory- Revised; PHQ-9: Patient Health Questionnaire; Y-BOCS:
676 Yale-Brown Obsessive-Compulsive Scale. Values for categorical and continuous variables are expressed in percentages and mean \pm
677 standard deviation (SD), respectively. Bold indicates a statistically significant difference.

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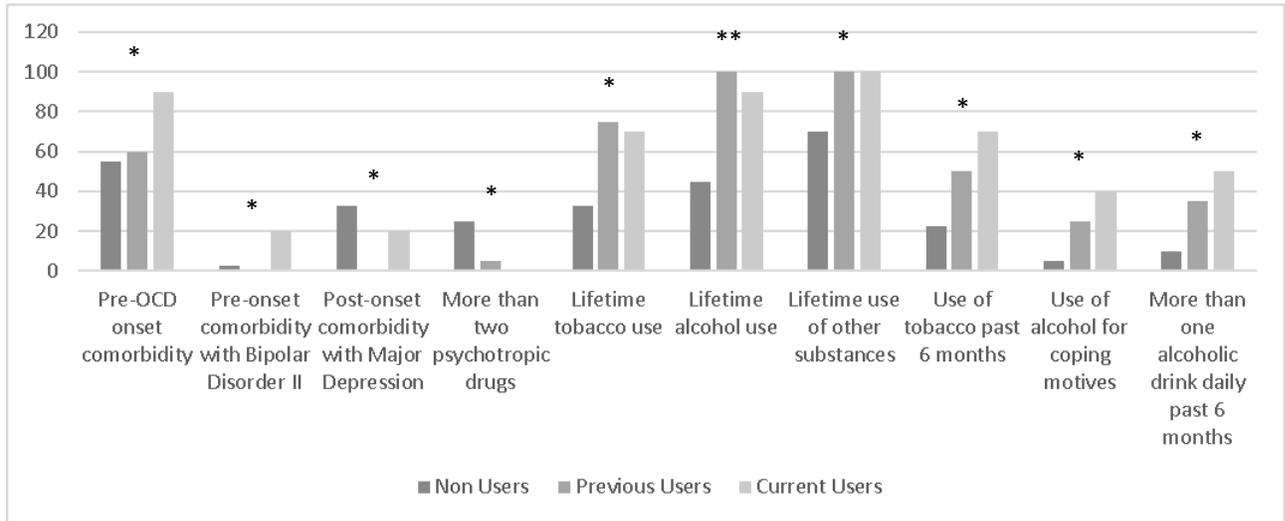
679

680 **Figures**

681 **Figure 1.** Statistically significant categorical variables in the comparison between non-users,
682 previous users, and current users of cannabis.

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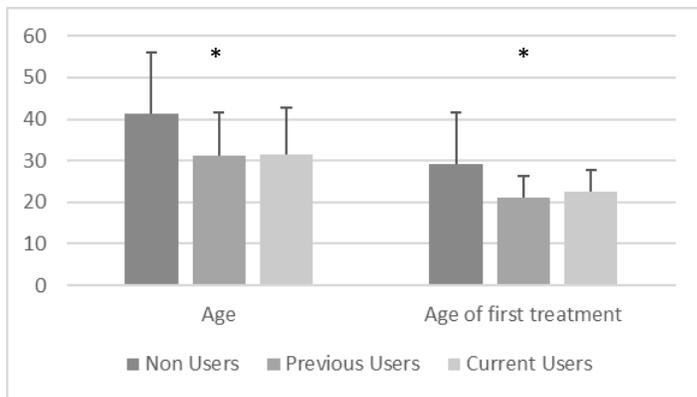
686

687 **Legend:** Values for categorical variables are expressed as %. OCD: obsessive compulsive disorder; statistics: *: p<.05;
688 **:p<.001.

689

690 **Figure 2.** Statistically significant continuous variables in the comparison between non-users,
691 previous users, and current users of cannabis.

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695 **Legend:** Values for continuous variables are expressed as mean ± standard deviation; statistics: * p<.05.