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CANNABINOID-INDUCED PSYCHOSIS: A CROSS-SECTIONAL GENDER STUDY

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SUMMARY

Background: *Gender is a crucial factor in the development of mental illnesses, with an essential influence on clinical characteristics and not only on the prevalence of each disorder. Gender differences in cannabinoid-related disorders are highlighted by different research fields (preclinical, clinical, socio-demographic studies), but few studies focused on differential symptom expression in cannabinoid-induced psychosis. This study aims at investigating qualitative and quantitative gender differences in specific psychopathological domains in a clinical sample of subjects affected by cannabinoid-induced psychotic disorder, without psychiatric comorbidity.*

Subjects and methods: *The study was carried out at the Psychiatric Inpatient Service of General Hospital of Perugia (Italy). In this cross-sectional gender study, 28 inpatients were enrolled, 14 males (M) and 14 females (F). Participants were administered a psychometric battery consisting of 7 tests (PANSS, NDS-I, YMRS, HAM-D, HAM-A, AQ, SSI) in order to investigate 7 psychopathological domains (Psychosis, Dysphoria, Mania, Depression, Anxiety, Aggressive Behaviour and Suicide Ideation). Scores obtained at each test were compared between male and females by using Mann-Whitney U test ($p<0.05$).*

Results: *In this study, we observed that males present higher severity of psychotic symptoms, with prominent scores in PANSS positive and general psychopathology scale ($p<0.001$), and an important expression of aggressive behavior ($p<0.001$) compared with females. Female sample, instead, shows a greater expression of dysphoria and depressive domains ($p<0.001$) and a lower, but statistically significant, prevalence in the anxiety domains expression ($p=0.01$). By these observations, we could assert that in male group thought disorders are prominent. On the other hand, in female group affective disorder are prominent.*

Conclusions: *This study confirmed how gender influences the phenomenic expression of psychiatric disorders. In line with the precision medicine paradigm, a further clarification of different clinical profiles based on gender would allow the choice of a personalized treatment plan with better efficacy and accuracy indices.*

Key words: *substance-induced psychosis - cannabinoids - gender differences – inpatients - gender medicine*

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INTRODUCTION

Gender is a very important factor in the development of mental illnesses with an essential influence on clinical characteristics and not only on the prevalence of psychiatric disorders (Carmassi et al. 2014). Despite this, few gender studies analyzed the differential clinical symptom expression in cannabinoid-induced psychosis. Emerging research shows that, although the prevalence of recreational use of cannabis remains higher in men, the prevalence gap between males and females is progressively decreasing (Chapman et al. 2017). Neurobiological factors interact in complex ways with environmental and socio-cultural aspects, which are strongly influenced by gender and which represent risk factors for psychopathology (Biancheri 2017, Ficini et al. 2012). It is interesting to report the recent acquisitions from preclinical studies: rodent females are more sensitive to the reward and gratification effects (Fattore et al. 2007) due to the CB1R agonist, they learn faster the self-administration of the CB1R agonist and with a higher dose, they are slower in ending the effect (Fattore et al. 2007) and have a higher recovery from stress when administration is stopped (Fattore et al. 2010). Females are more sensitive to acute sedation, antinociceptive effects, motor effects, while males are more sensitive to hypothermia and hyperphagia (Craft et al. 2013). High doses of tetrahydrocannabinol (THC) produce a greater anxiety effect in the female and an increased locomotor activity (Wiley 2003). Moreover, females develop a greater tolerance and show more symptoms of abstinence (Wakley et al. 2015). Numerous preclinical data demonstrate sex differences in the endocannabinoid system. Male rodents have a higher CB1R density in most regions of the brain, except in the amygdala where females have a greater number of CB1R receptors (Castelli et al. 2013). On the other hand, despite having a lower CB1R density, females show greater receptor activity (Mateos et al. 2011), greater desensitization after chronic exposure to cannabis (Burston et al. 2010) and an alteration of CB1R expression (Silva et al. 2016) compared to males. Interestingly, preclinical studies show that early childhood stress has specific effects on sex on the endocannabinoid system by increasing the expression of CB1R in females and decreasing its expression in males (Alteba et al. 2016). Another research group studied the differences in the density and function of cannabinoid receptors in ovariectomized rodents compared to females with normal ovarian cycle and males and reported that females with ovarian cycle have

a lower density of CB1R in the prefrontal cortex and amygdala compared to ovariectomized males and females (Castelli et al. 2014).

Among regular cannabis users, females reported greater tolerance and more frequent and severe withdrawal symptoms than males (Cuttler et al. 2016), and these symptoms are more predictive of recurrence. Females reported more frequently gastrointestinal symptoms such as nausea, abdominal discomfort and behavioral effects such as anxiety, irritability and agitation (Sherman et al. 2017, Schlienz et al. 2017), while men experienced gooseflesh, craving and sleep disturbances (Cuttler et al. 2016).

The greater positive reinforcement effects of cannabis use in combination with the negative reinforcement effects with severe withdrawal symptoms may explain why females experience faster progression of cannabis use disorders than males. Using data from the 2001-2002 National Epidemiological Survey on Alcohol and Related Conditions (NESARC n=43.093), Khan showed that while cannabis use disorder is more prevalent in males, females show a more rapid transition from first use to cannabis use disorder (Khan et al. 2013). This phenomenon, called "telescoping", has been reported in several studies (Ehlers et al. 2010) and has been observed for other addictive behaviors. Cannabis use may be associated with an earlier onset of psychosis in women than in males (Allegri et al. 2013). Typically, the age of onset of psychosis is later in females (Skosnik et al. 2006), Donoghue and his group have shown that this gender gap is narrowed in cannabis users (Donoghue et al. 2014).

Similarly, another group observed that while in casual consumers the risk of developing psychosis is higher in male individuals; in chronic consumers, the same risk is significantly higher in the female gender (Compton et al. 2009). Currently, the data collected strongly suggest that the use of cannabis, perhaps in accordance with other vulnerability factors, can counteract the late onset of psychosis in women (Nia 2018). The early onset of psychosis is associated with a worse prognosis; as female may be more sensitive to the potential effects of cannabis on the onset of psychosis, particular attention should be paid due to the increasing exposure to cannabis among females (Nia 2018). Anxiety and mood disorders occur in higher percentages in females with cannabis-related disorders than in males (Khan et al. 2013). Females with cannabis use disorder in late adolescence and early adulthood have higher rates of anxiety and suicide risk than males (Foster et al. 2016).

A retrospective study seems to confirm a greater sensitivity of the female gender to cannabinoids, especially if there are substances with higher THC concentrations; they required an early start of treatment and a higher pharmacological concentration (Nia et al. 2019).

Cannabis/THC intoxication can trigger acute paranoid psychosis in some consumers (Murray et al. 2007). Furthermore, the use of cannabis can worsen the course of a pre-existing persistent psychotic disorder, with a recurrence and/or worsening of the symptoms (especially positive ones), leading to possible higher risk of hospitalization (Foti et al. 2010).

Schizophrenia patients who have history of cannabis use were demonstrated to present with the first psychotic episode at a younger age (Large et al. 2011). Recent research showed that there is a clear relationship between the frequency of use of cannabis and the chances of developing a psychotic disorder (Di Forti et al. 2009). The risk related to the onset of mental disorders also depends on the age of the first use. The risk is higher for those starting in early adolescence than for consumers starting in adulthood (McGrath et al. 2010). Cannabis use does not only predict a psychotic onset but is also associated with the expression of a sub-threshold psychosis, both in the form of schizotypal traits and subclinical psychotic experiences (Van et al. 2002). There is modest evidence that self-medication can play a role although because the association between cannabis and psychosis cannot be wholly reduced to this effect: statistically correct studies on the effect of self-medication have found an increase in risk between cannabis use and psychosis outcome.

People who have an acute psychotic episode after cannabis use, and who have needed treatment, are at high risk of developing a persistent psychotic disorder over time (Arendt et al. 2005). In a recent Finnish study, 46% of people who had been hospitalized for cannabis-induced psychosis developed schizophrenia over the next 8 years (Niemi-Pynttäri et al. 2005).

Many epidemiological studies have described a significant association between cannabis use and psychosis, although only a minority of people who use cannabis will then develop a psychotic disorder. Nevertheless, the global number of people who have used cannabis at least once has been estimated at between 149 and 190 million (UNODC 2009), therefore, this minority susceptible to psychosis represents a significant number of people. Furthermore, the proportion of schizophrenia attributable to the use of cannabis is estimated between 8% and 15% (Henquet et al. 2005), therefore susceptible to potential preventive measures.

Our study aims to highlight the presence of any qualitative and quantitative gender differences in specific psychopathological domains expression belonging to a clinical sample of subjects affected by cannabinoid-induced psychotic disorder, without psychiatric comorbidity.

SUBJECTS AND METHODS

In this cross-sectional gender study, 28 inpatients were enrolled, 14 males (M) and 14 females (F), with an age range between 18 and 62 years with an average age of 35.6 years. Subjects were recruited during their hospitalization at the Psychiatric Inpatient Unit of the General Hospital of Perugia (PG), Umbria, Italy. Recruitment started in January 2017 and ended in November 2019.

Inpatients included in the study were aged 18-65 and affected by substance-induced psychotic disorder, with particular reference to cannabinoid abuse, according to the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association 2013).

The following exclusion criteria were set: non-Italian nationality, positivity to toxicological tests for different or additional substances other than THC, positive history for serious mental illnesses and/or from moderate to severe neurocognitive disorders.

Eligible subjects underwent a thorough clinical-anamnestic investigation. In addition to the information and anamnestic sources, potentially recruitable inpatients were subjected to psychometric screening, as part of the department routine evaluation. This screening focused on the administration of the following tests: DSM-5 Structured Interview for Disorders, Clinician Version (SCID-5 - CV), to exclude major psychiatric disorder; the Structured Clinical Interview for DSM-IV (SCID-II) (First et al. 1997) and the Minnesota Multiphasic Personality Inventory questionnaire (MMPI-II) (Butcher et al. 1989) to investigate the presence of any personality disorder.

Information schedules concerning purposes of the study were submitted to candidates together with the informed consent form.

After obtaining consent, the subjects underwent a psychometric battery consisting of 7 tests one for each psychopathological domain. To study dysphoria we have chosen the Neapen Dysphoria Scale – Italian Version (NDS-I) (Berle and Starcevic 2012; D'Agostino et al. 2016), the Positive And Negative Syndrome Scale (PANSS) (Stanley et al. 1987) for psychotic domain, Hamilton Depression Rating Scale (HAM-D) (Hamilton 1960) for depressive domain, Hamilton Anxiety Rating Scale (HAM-A) (Hamilton 1959) for anxiety domain, Young Mania Rating Scale (YMRS) (Young et al. 1978) for mania domain, Aggressive Questionaire (AQ) (Buss & Perry 1992) for aggressive behaviour domain and the Scale for Suicide Ideation (SSI) (Beck 1979) for suicide ideation domain. Of these, 2 tests (NDS-I and AQ) were self-administered questionnaires, while the remaining 5 were administered by adequately trained clinicians (PANSS, HAM-D, HAM-A, YMRS, SSI).

Data were then extracted and inserted into a specific dataset created using the Statistical Package for Social Sciences (SPSS), v. 20. After setting a statistical significance level $p<0.05$, arithmetic averages obtained for each test score, in relation to the single gender, were compared using the non-parametric test U of Mann-Whitney for hypothesis testing.

RESULTS

The sample was composed of of 28 subjects, 14 males and 14 females. Mean scores at the administered tests were obtained for the whole sample and for both male and female gender (Table 1).

The following linear diagrams (Figure 1 to Figure 10) show the distributions of the scores obtained by the individual subjects for each type of test.

Observing the scores obtained by the two subgroups at the PANSS we can observe a clear difference in the distribution of the total score (Figure 2), in the scale of positive symptoms (Figure 3) and in the general psychopathology' ones (Figure 5). This difference shows a prevalence, or at least a greater intensity, of positive symptoms in the male group. As for the scale of negative symptoms (Figure 4), however, the data are substantially overlap.

Table 1. Mean scores at the administered tests

Gender	µAge NDS-I	µNDS-I	µHAM-D	µYMRS	µAQ	µPANSS tot	µPANSS pos	µPANSS neg	µPANSS psigen	µSSI	µHAM-A
Whole sample	35.6	55.5	9.9	12.5	88	72.7	18	10.2	44.6	16.1	5
Male	37.3	44.4	6.2	13.2	103.1	91.5	22.9	9.9	59.1	18.7	12
Female	33.9	66.6	13.5	11.7	73	53.9	13.1	10.6	30.1	13.4	18

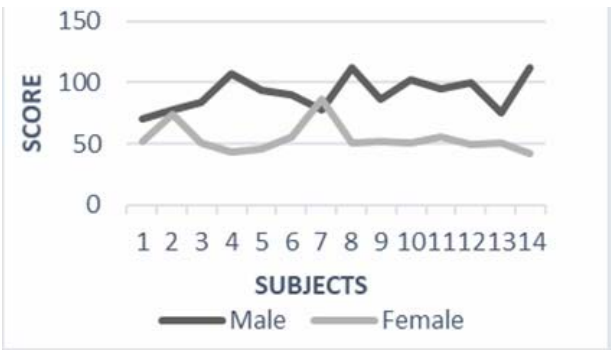

Figure 1. PANSS total score

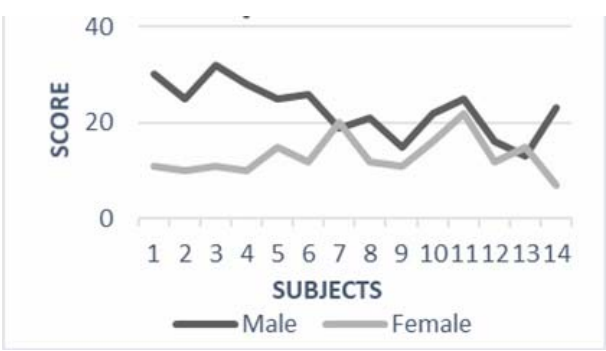

Figure 2. PANSS positive scale

By analyzing the scores relating to the dysphoria domain in the two groups (Figure 6), we can appreciate a greater preponderance of this symptomatology in the female group. This difference does not appear in the distribution relative to the mania scores (Figure 7), where the data tend to overlap.

Looking at the scores on the Hamilton scales for depression (Figure 8) and anxiety (Figure 9) respectively, we note that in both cases there are differences in the distribution of the scores. In particular, for the depression scale we note a prevalence of the female group. On the contrary, in the scores relating to the anxiety scale there is a male preponderance.

A prevalence of the male group can also be observed in the domain of aggression (Figure 10). Finally, the difference in suicidal ideation appears more dubious. Despite an initial difference for the benefit of the female population, the data tend to converge at the end of the graph.

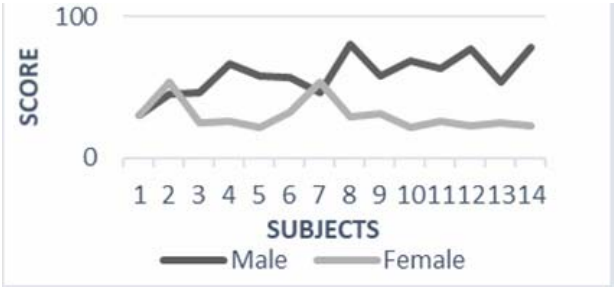

Figure 3. PANSS psychopathology scale

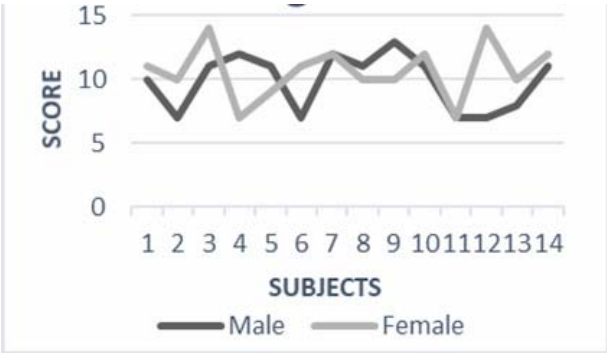

Figure 4. PANSS negative scale

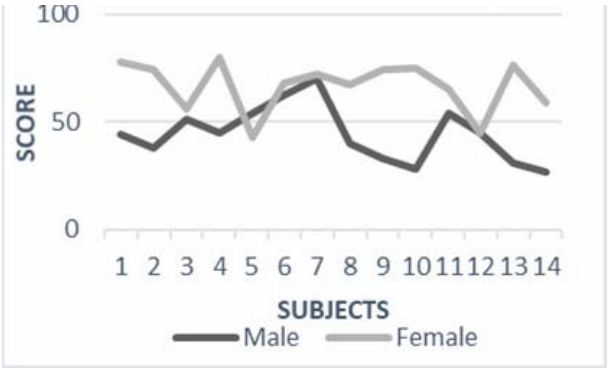

Figure 5. NDS-I total score

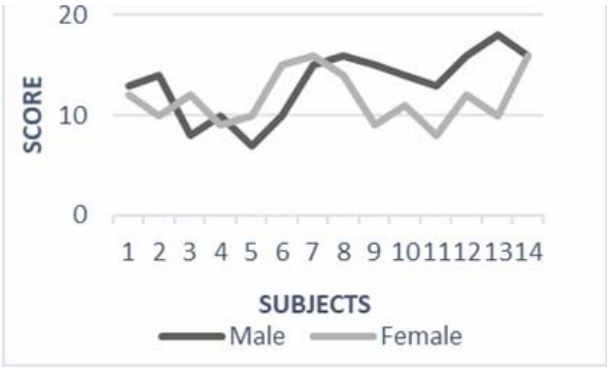

Figure 6. YMRS total score

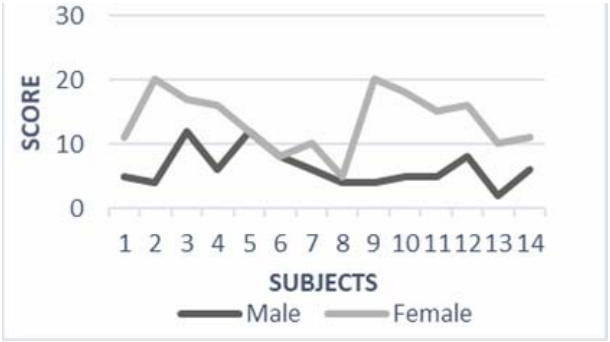

Figure 7. HAM-D total score

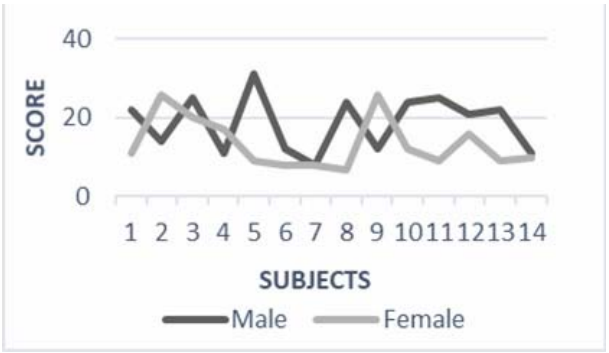

Figure 8. HAM-A total score

Table 2. Psychopathological domains

	NDS Total Score	HAM-D	HAM-A	YMRS	AQ	PANSS tot	PANSS pos	PANSS neg	PANSS psgen	SSI
U Mann-Whitney test	21.0	20.5	29.5	69.5	40.5	6.5	15.0	84.0	11.5	55.0
2 tails Sig. Asint.	0.00	0.00	0.01	0.19	0.01	0.00	0.00	0.51	0.00	0.05
Exact Statist. Signif. (p<0.05)	*<0.001*	*<0.001*	*0.01*	0.19	*<0.001*	*<0.001*	*<0.001*	0.54	*<0.001*	0.05

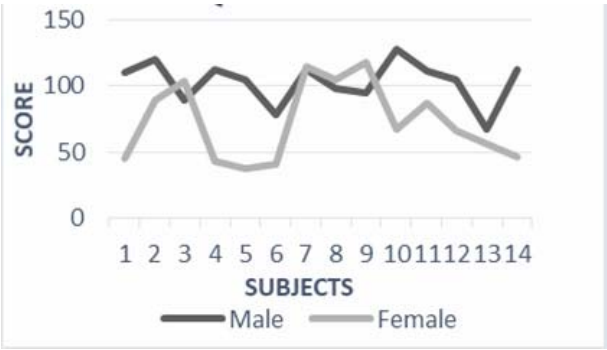

Figure 9. AQ total score

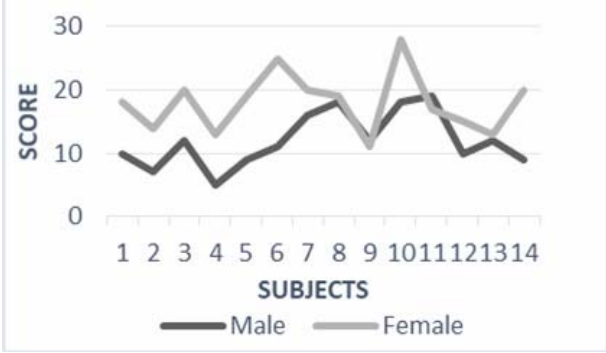

Figure 10. SSI total score

The aspects highlighted in the analysis of the previous graphs were confirmed by the statistical processing carried out using the Mann-Whitney U test. The reported results (Table 2) show psychopathological domains that are statistically significant. It should be noted that the significance relating to suicidal ideation is limited.

DISCUSSION

In this study, we observed that males present higher severity of psychotic symptoms, with prominent scores in PANSS positive and general psychopathology scale ($p<0.001$), and an important expression of aggressive behavior ($p<0.001$) compared with females. Female sample, instead, shows a greater expression of dysphoria and depressive domains ($p<0.001$) and a lower, but statistically significant, prevalence in the anxiety domains expression ($p=0.01$). By these observations, we could assert that in male group thought disorders are prominent. On the other hand, in female group affective disorder are prominent. This study has several limitations. First, the small size of the analyzed sample, which does not ensure statistical power to avoid incurring α type I errors. Furthermore, it was not possible to evaluate inter-rater reliability. In addition, the test battery was administered during the post-acute phase and for each subject this period varies over time. This could have led to underestimate or overestimate some symptomatic expressions in some subjects compared to others. A further bias could also derive from the intake by the analyzed subjects of substances other than cannabis and not detectable by toxicological tests (New Substances of Abuse).

CONCLUSIONS

This study, which acts as a contribution to research on gender medicine in mental health, confirmed how gender influences the phenomenal expression of these disorders. Precisely in this perspective, although the data presented are only preliminary, it is justified to deepen the differential symptomatic profile highlighted. If these data were confirmed by future studies with greater statistical power, then we could obtain numerous advantages. These would not be represented by mere gnoseological contributions, but especially clinical ones. In line with precision medicine paradigm, having a better clarity on symptomatic variations based on gender would allow the choice of a personalized treatment plan with better efficacy and accuracy indices.

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Conflict of interest: *None to declare.*

Contribution of individual authors:

Massimo Claudio Bachetti conceived and designed the study.

Massimo Claudio Bachetti & Francesca Scopetta wrote the first draft of the manuscript.

Massimo Claudio Bachetti & Roberta Lanzi performed statistical analyses.

Massimo Claudio Bachetti, Roberta Lanzi, Giulia Menculini & Patrizia Moretti visited patients and carried out clinical work.

Massimo Claudio Bachetti, Roberta Lanzi conducted testing.

Massimo Claudio Bachetti, Roberta Lanzi, Francesca Scopetta, Giulia Menculini, Patrizia Moretti & Alfonso Tortorella discussed results,

Giulia Menculini, Patrizia Moretti & Alfonso Tortorella supervised the writing of the manuscript; all authors approved the final version of the manuscript.

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