



Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

The interaction of gender and cannabis in early phase psychosis

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ARTICLE INFO

Article history:

Received 28 December 2016

Received in revised form 25 April 2017

Accepted 28 April 2017

Available online xxxx

Keywords:

Cannabis

Cannabis use disorder

Early phase psychosis

Gender

Female

Marijuana

ABSTRACT

Cannabis is the third most common recreational drug used world-wide after tobacco and alcohol. Globally, cannabis legalization is becoming more common. In light of its known link to psychosis development, it is imperative that we are well-informed regarding the impact of cannabis on the course of psychosis, in both males and females. However, the majority of the work to date on the role of cannabis in psychosis outcomes has not had a gender focus, important when considering patient specific treatments. This review examines what is currently known, from gender focused studies, about the interaction of gender, cannabis use and psychotic disorders.

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1. Introduction

Early phase psychosis (EPP) intervention programs are focused on the 'critical period' of illness that is defined as up to the first five years of illness (Birchwood et al., 1998) and comprised of integrated pharmacological and psychosocial interventions (Jeppesen et al., 2005; Malla et al., 2005; Mueser et al., 2013; Yung and McGorry, 1996). These EPP programs generally treat individuals from 16 to 35 years of age and have been shown to have superior effectiveness on outcomes in comparison with routine care, including high rates of symptomatic remission (Bertelsen et al., 2008; Harvey, 2007; Malla et al., 2006; Nordentoft et al., 2009). The profiles of disease impact differ significantly between males and females with female patients generally being viewed as having superior outcomes as compared to male patients.

However, these positive outcomes for both genders are compromised by the high rate of cannabis use in EPP (Carr et al., 2009; Gonzalez-Pinto et al., 2011; Harrison et al., 2008). Multiple lines of evidence have indicated that cannabis use, particularly during the important phase of adolescent brain development, may be a risk factor for the development of EPP in those individuals sensitive to a gene × environment interaction. Starting with the Swedish longitudinal study (Andreasson et al., 1987), epidemiological evidence has accumulated

supporting the theory that cannabis use may play a causal role in the development of psychosis (Arseneault et al., 2002; Casadio et al., 2011), that initiation of regular cannabis use in adolescence is associated with a younger age of onset of psychosis (Casadio et al., 2011; Kuepper et al., 2011; Malone et al., 2010), and that these may be dose-response positive relationships. With respect to treatment, EPP cannabis users do not maximally benefit from the early intervention service (EIS) framework (McGrath et al., 2010); experiencing greater severity of symptoms (Owen et al., 2011; Renard et al., 2014), higher risk of relapse (Schoeler et al., 2016a, 2016b), reductions in medication adherence (Miller et al., 2009), and global functioning deficits (Peralta and Cuesta, 1992). It is thus significant that regular cannabis use diminishes the gains that can be made to the recovery in EPP.

Cannabis is the most common illegal recreational drug used world-wide by youth ages 18–25 (Crime, 2016). Cannabis use disorders (CUD) have an estimated prevalence from epidemiological surveys in the USA, Canada and Australia of 1–2% of adults in the past year and 4–8% of adults during their lifetime, with higher rates of abuse of or dependence on cannabis in males than females (Pearson et al., 2013; WHO Management of Substance Abuse unit, 2016). In the age bracket associated with onset of EPP, under 25 years of age, significant numbers of both males and females report past year cannabis use (Adamson, 2013; Canada, 2012; Crime, 2016). When the EPP population is surveyed regarding cannabis use; lifetime experience >80% is seen (Sembhi and Lee, 1999; Van Mastrigt et al., 2004). Interestingly, there is evidence of equal rates of use among males and females in EPP populations, though these are not well explored (Gonzalez-Pinto et al., 2011). At entry to care, approximately 30% of EPP patients meet criteria for substance abuse/dependence with cannabis being the most

Abbreviations: CUD, cannabis use disorder; EPP, early phase psychosis; DUP, duration of untreated psychosis; EIS, Early intervention services.

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<http://dx.doi.org/10.1016/j.schres.2017.04.046>

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Please cite this article as: Crocker, C.E., Tibbo, P.G., The interaction of gender and cannabis in early phase psychosis, Schizophr. Res. (2017), <http://dx.doi.org/10.1016/j.schres.2017.04.046>

commonly misused substance (Carr et al., 2009; Harrison et al., 2008; Myles et al., 2016).

The focus of this article is on examining the role the interacting factors of gender and cannabis use have on the outcomes seen in early phase psychosis. While this is a thematic review, we did a comprehensive review of several databases to locate the sources for this discussion. We identified eligible studies through an electronic search of Web of Science, PubMed and Embase with the combinations of the following terms: cannabis, cannabinoids, psychosis, gender, sex, marijuana, marihuana, and smoked marijuana. No time limit was placed on the search but articles were limited to those in English or with an English translation and published in a peer reviewed journal. Stimulant induced psychosis, and studies that were not using early phase psychosis populations were excluded. Examining gender differences is a more recent, but important, focus of investigation in order to improve treatment delivery in EPP. The small body of research in this area assembled to date, and our own preliminary findings, suggest that women with EPP and CUD may present with a more challenging treatment profile than even male EPP with co-morbid CUD, thus suggesting a different approach in treatment. To explore this fully, we have focused this review on studies that specifically employed gender as a variable in the design of the work. Reviewing studies that have examined gender differences in EPP and CUD separately will allow context for discussion of potential gender \times CUD \times EPP interaction.

2. EPP and gender

There is not a high degree of consensus as to which clinical differences present between female and male EPP patients. There is even some debate about the prevalence of psychosis in males compared to females (Filatova et al., 2016; Ochoa et al., 2012) which may be in part due to more affective symptoms present in EPP females, reflected in a larger proportion of females diagnosed with schizoaffective disorder (Filatova et al., 2016). This may be influenced by the diagnostic criteria used as some are more sensitive to affective symptoms than others, potentially influencing the ratio of EIS males to females reported (Ochoa et al., 2012). However, when non-affective psychosis is clearly outlined in the methodology, a ratio of 2/3 males to 1/3 females in EIS is generally consistent (Baldwin et al., 2005; Hafner et al., 1998; Kirkbride et al., 2016). Interestingly, two large epidemiological studies have reported an increasing risk of females developing psychosis over recent decades, yet this has not been reflected in any changes to the male:female EIS ratio to date (Filatova et al., 2016; Kuhl et al., 2016).

Some studies report no EPP gender differences in clinical profile (Zhang et al., 2012), while it has also been suggested that there may be a continuum of gender influences over the course of schizophrenia; few gender differences observed in ultra high risk youth with emerging differences between genders in EPP, and then definite gender differences in more established schizophrenia (Barajas et al., 2015; Ochoa et al., 2012). Relevant to this review, the magnitude of any differences between male and female EPP in clinical outcomes may be influenced by the degree of substance use, as exclusion of substance-dependent patients results in studies with fewer gender differences reported (Segarra et al., 2012).

Several studies report an earlier onset of illness of approximately three years in males as compared to females (Chaves et al., 1993; Dekker et al., 2012; ElTayebani et al., 2014; Hafner et al., 1998; Hui et al., 2016; Szymanski et al., 1995), however, this is not always a consistent finding (Andia et al., 1995; Kirkbride et al., 2016; Thorup et al., 2007). The duration of untreated psychosis (DUP) has also been reported to be longer in males than in females in some studies. This may have a basis in pathways to care differences, where females will turn more often to a partner or close family members for help seeking whereas males do not (O'Callaghan et al., 2010). This may in turn account for the significantly larger percentage of males found in the community with undiagnosed psychosis (Michel et al., 2016). However, two meta-

analyses specifically addressing this question did not show a gender difference in DUP (Cascio et al., 2012; Szymanski et al., 1995).

There are some documented gender differences in symptoms in EPP. Males at entry to EIS have generally been found to have more negative symptoms and more violent behavior while females are more likely to have affective symptoms including anxiety (Drake et al., 2016; Hui et al., 2016; Segarra et al., 2012; Szymanski et al., 1995; Thorup et al., 2014; Tseliou et al., 2015). Using a SADS-C scale, Szymanski et al. (1995) reported that female patients had more inappropriate affect and bizarre behavior than males (Szymanski et al., 1995). Other studies have shown more suicide attempts for females, but greater numbers of successful suicides in males (Cotton et al., 2009; Thorup et al., 2007). A recent study examining trends for suicide in schizophrenia over a 20 year period found that this pattern may be specific to EPP, and later in the illness females are more at risk of suicide while the risk for males declines (Kaplan et al., 2016). Less consistently, females have reported to have more positive symptoms which may have important implications for disease trajectory as in females, the higher the positive symptom score on the positive and negative syndrome scale (PANSS), the greater the impairment in social performance (Chaves et al., 1993; Thorup et al., 2007). One study reported a greater proportion of diagnoses of paranoid schizophrenia in females as compared to males but this has only been replicated in one study and in chronic, not EPP, patients (Andia et al., 1995; Zhang et al., 2012). Fikreyesus et al. (2016) reported the odds of a relapse was not significantly different between males and females (Fikreyesus et al., 2016); however, another group reported that after one year of treatment, males still presented with more violent tendencies and females were more likely to have experienced a hospitalization (Tseliou et al., 2015).

Female EPP patients have been characterized as having better social functioning at all stages of EPP. The earlier age of onset for men may play a role in these outcomes as males will develop psychosis at an age coinciding with the period of greatest psychosocial development, and consequently, their overall functioning might be disrupted to a greater extent than females who are often in their early to mid-twenties when they develop psychosis. Female EPP are more likely to be married; and more likely to have children both at illness onset and after years of treatment (Andia et al., 1995; Chaves et al., 1993; ElTayebani et al., 2014; Hafner et al., 1998; Thorup et al., 2014). At entry to EIS, males are reported to be less likely employed, and living independently than females (Chaves et al., 1993; Hui et al., 2016), a trend that may remain after years of treatment (Thorup et al., 2014). After treatment, females often have better scores on global functional assessments, are more likely to be living with family and have less unemployment when compared to males at the same point in their illness course (Andia et al., 1995; Cotton et al., 2009). Using the disability assessment scale, Vazquez-Barquero in their Cantabria cohort of first episode patients reported that males had a worse overall disability (Vazquez-Barquero et al., 1999). Males also more commonly had substance abuse concerns at entry that can persist through the course of treatment (Cotton et al., 2009; Thorup et al., 2014, 2007).

There are very few gender differences in neurocognition in EPP reported and there is controversy surrounding whether these differences are truly present. A clear pitfall to this research is the inability to blind researchers to gender. Generally, female EPP perform better on executive function and verbal learning tasks than male EPP patients, but did not differ significantly from female healthy controls. Several studies showed gender differences in neuropsychological testing that were consistent with what was seen among healthy controls (Albus et al., 1997; Ayesa-Arriola et al., 2014; Ittig et al., 2015). Other studies showed males tended to have better neurocognitive performance in the visual domain (Hui et al., 2016), and also in working memory tasks (Ittig et al., 2015) as compared to female EPP. On the whole, the portrait of cognition in the setting of gender and EPP is not clear.

Generally, more females achieve full remission as compared to males with treatment (Szymanski et al., 1995; Thorup et al., 2014).

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