Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Behavioral Sciences

Sex differences in drug-induced psychosis

Adrianna Mendrek[1,2] and Liana Fattore[3]

Men and women affected by schizophrenia display different age of onset, symptom profile and course of the disease. Similarly, men and women differ in the prevalence and frequency of drug use, pattern and reasons of use, and vulnerability to develop drug addiction. An understanding of the role of sex in modulating brain processes and behavior in patients with substance use disorder and/or schizophrenia-like symptoms has broad implications for gender-tailored treatment approaches. Cognizant of the considerable recent evidence for sex and gender differences in drug addiction and schizophrenia, we focused this review on the sex-dependent differences in drug-induced psychosis and on factors that may contribute to such male–female differences.

Addresses
[1] Department of Psychology, Bishop's University, Sherbrooke, QC, Canada
[2] Department of Psychiatry, Université de Montréal, Montreal, QC, Canada
[3] CNR Neuroscience Institute-Cagliari, National Research Council-Italy and Centre of Excellence ''Neurobiology of Dependence'', Cittadella Universitaria, Monserrato, Cagliari, Italy

Corresponding author: Fattore, Liana (lfattore@in.cnr.it)

Current Opinion in Behavioral Sciences 2017, **13**:152–157

This review comes from a themed issue on **Addiction**

Edited by **Scott Edwards** and **Karen D Ersche**

For a complete overview see the Issue and the Editorial

Available online 23rd December 2016

http://dx.doi.org/10.1016/j.cobeha.2016.11.019

Introduction

According to the World Drug Report 2016, a majority of people using illicit substances are males, while females are more likely to (mis)use prescription drugs like tranquilizers and sedatives [1]. However, this gender gap is narrowing especially among the young population and in advanced countries [1]. Men and women differ also in terms of (i) processing reward and development of drug addiction [2], (ii) propensity to become addicted to non-drug rewards [3], and (iii) ability to control impulses and motivational states [4,5•]. Drug pharmacokinetics and pharmacodynamics [6], drug availability [7•], neurobiological factors [8], sociocultural and environmental influences [9•] and different risk-based decision making skills in males and females [10], all may contribute to sex differences in drug use.

Drug addiction comorbidity is frequent among schizophrenia patients [11]. Population-based studies reported the male gender among the significant predictors of comorbid substance use disorders in patients with schizophrenia [12]. Schizophrenia remains one of the most puzzling psychiatric disorders, but at least today it is clear that there are important sex/gender differences in the predisposition and expression of this disorder [13,14]. The incidence of schizophrenia is generally higher in men than in women, while the prevalence is higher in men during the first half of life and in women after 40 years of age [15,16]. Following the diagnosis men show more prominent negative symptoms, such as social withdrawal and blunted affect, whereas women appear to exhibit more positive and affective symptoms, such as depression, inappropriate affect and sexual delusions [13,15]. Finally, women tend to respond better to treatment with antipsychotic medications, but they present with more severe drug side effects [17•].

In the following paragraphs, we will first illustrate and discuss clinical findings revealing a moderating role of gender in drug-induced psychosis. Then, we will review preclinical evidence for sex-dependent differences in the manifestation of drug-induced psychotic symptoms in animals, and conclude with the analysis of the potential protective and risk factors determining different vulnerability to psychosis in males and females. We hope this article will mobilize medical and scientific attention to the need for gender-specific treatment approaches for patients with addiction and psychosis, and ultimately stimulate research and activities in the field.

Role of gender in drug-induced psychosis: clinical studies

Drug-induced psychoses are present only in a small proportion of individuals and out of these only some will develop schizophrenia or related psychotic disorders. The occurrence of drug-induced psychosis depends on various factors including: duration and intensity of drug use, age at first use, type of drug used and potentially other demographic (e.g., socio-economic status), psychological (e.g., presence of mood and anxiety symptoms), and genetic factors (e.g., being at high risk to develop schizophrenia because of its presence in a first-degree relative). The studies vary mainly as a function of a given drug and severity of abuse/dependence.

Cannabis

Several lines of evidence have linked cannabis abuse to the subsequent development of schizophrenia-spectrum disorders and to the presence of sub-clinical psychotic

symptoms [18,19]. Sex/gender does not seem to be related to the age at onset of cannabis-induced psychosis (unlike primary psychosis), but in a 3-year follow-up study of over 500 cases of cannabis-induced psychosis, men had much higher rates of transition to schizophrenia-spectrum disorders (48%) than women (30%), and the risk was higher in younger relative to older men [20]. More recently, Patel *et al.* [21] investigated a sample of over 2000 first-episode psychosis and found that 46% were using cannabis. Cannabis use was associated with being young, male and single and with increased number of hospitalizations over a 5-year follow-up.

Psychomotor stimulants

It is well documented that the use of cocaine and amphetamines is associated with increased risk of experiencing psychotic symptoms and the abuse of these drugs often predates the onset of schizophrenia [22,23]. The literature concerning gender is scarce. Mahoney *et al.* [24] made explicit comparisons between sex/gender in cocaine-dependent and in methamphetamine-dependent individuals. Overall, relative to men, women reported more frequently various types of hallucinatory experiences (e.g., auditory, tactile, olfactory) and delusions (e.g., paranoia) both during the drug use and while abstinent. These results were somewhat inconsistent with an earlier report by Mooney *et al.* [25] who examined subjective and physiological responses to smoked cocaine in male and female users. In that study, 67% of participants reported feeling paranoid/suspicious in response to cocaine in the laboratory setting, but the ratings were higher in men than in women, in line with a retrospective study by Brady *et al.* [26] who found that relative to women, cocaine-dependent men were more likely to develop psychosis. One explanation for this inconsistency might be that in the Mahoney *et al.* [24] study, both sexes reported using similar quantities of stimulants, which could result in the overall greater blood and brain levels in women than in men due to differences in average weight and rate of metabolism. In the previous study by Mooney *et al.* [25] plasma cocaine levels were measured and did not differ between the sexes. Undoubtedly, more studies are needed in this field.

Primary versus substance induced psychosis

Despite very high comorbidity, schizophrenia and drug addiction are typically studied separately, and very little has been reported in terms of differences between men and women diagnosed with psychotic disorders and concurrent drug use. One exception to this general trend is the study by Caton *et al.* [27] who compared patients with primary psychotic disorders with concurrent substance use and those with substance-induced psychosis. The results revealed that in both groups women had better premorbid adjustment than men, but showed greater depression, history of sexual abuse and comorbidity with post-traumatic stress disorder (PTSD). Consistently with numerous other reports, the age at admission was lower for men relative to women with primary psychosis (26 vs. 30 yrs.), but there was no sex-dependent difference in the drug-induced psychosis group (30 yrs. for both sexes). Conversely, there was no difference in the age at onset of a regular drug use between men and women with the primary psychosis (17–18 yrs.), but in the group of drug-induced psychosis it was men who started using earlier than women (18 vs. 21 yrs) and thus had a longer exposure before developing drug-induced psychosis. It is clear that we need more studies examining these complex interactions.

Role of sex in drug-induced psychosis: animal studies

Animal models are essential tools in scientific research and in medicine, including psychiatry. Predictive and reliable animal models for complex psychiatric disorders, such as addiction and schizophrenia, are indispensable for understanding the neurobiological basis of the disorder and for developing more effective pharmacological tools. A great progress has been made during the last years in the development and characterization of reliable animal models of addiction, which revealed significant sex differences in many aspects of addictive behavior and vulnerability factors like impulsivity and compulsivity [28]. Sex-dependent differences have been described also in animal models of schizophrenia and other psychiatric disorders [29] and, at least in part, have been attributed to the different hormonal asset of the two sexes [30••]. Figure 1 summarizes the most common sex-dependent differences reported in drug addiction, schizophrenia and drug-induced psychosis.

In a neurodevelopmental model of schizophrenia, sex-specific differences have been recently reported in rats prenatally exposed to methylazoxymethanol (MAM) acetate, where female rats were found to consume more alcohol than males [31]. Almost all current rodent models of schizophrenia (i.e. developmental, pharmacological, environmental or obtained following lesions or genetic manipulation) include sensorimotor gating deficits. Due to its high cross-species neurobiological homology, the prepulse inhibition of the acoustic startle reflex (PPI) is now a common test to study drug-induced psychosis. A reduced PPI is consistently observed in schizotypal subjects, schizophrenic patients and their relatives, and has been therefore proposed as an endophenotype of schizophrenia [32]. Sex differences in PPI have been described in human studies [33], healthy women showing higher startle response than healthy men and schizophrenia women displaying greater response amplitude than affected men [34]. Curiously, schizophrenia men show less PPI than healthy men, while schizophrenia women show a PPI similar to that of healthy women [35,36]. Importantly, PPI fluctuates across the menstrual cycle in healthy women, reaching the lowest levels during the