Gender Differences and NPS

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Sex and gender deeply affect the subjective effects and the pharmaco-toxicological responses to drugs. Men are more likely than women to use almost all types of illicit drugs and to present to emergency departments for serious or fatal intoxications. However, women are just as likely as men to develop substance use disorders, and may be more susceptible to craving and relapse.

Keywords: Gender/sex differences ; novel psychoactive substances ; male/female differences in response to drugs

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Men and women differ in terms of physiology and pathophysiology. Male/female differences are important in medicine, and can be responsible for sex-specific clinical manifestations and response to therapies. Sex differences in bioavailability, distribution, metabolism and eliminations of drugs can affect their efficacy and safety and some drugs may be more effective in women than in men, or vice versa[1]. Sex-related differences have been demonstrated for many drugs[2][3][4], including drugs of abuse[5]. Clinical and preclinical studies provided compelling evidence of hormonal- and sex-dependent differences in the wanted and unwanted effects of recreational drugs[6][7][8][9] and in drug sensitivity[10], which may result in a different likelihood of seeking and taking drugs on future occasions and in a different proneness to develop dependence[11]. Socially gendered factors (e.g., social stigma) may also interact with biological factors in modulating drug consumption and the efficacy of therapeutic interventions[12]. According to the last World Drug Report (WDR 2020), drug use is more prevalent among males than females; yet, women are more affected than men by the non-medical use of sedatives and tranquillizers, and substance use disorders are more prevalent in female than in male prisoners[13].

Over the last decade, an incredibly high number of novel psychoactive substances (NPS) have emerged as alternatives to regulated drugs, and new ones are continuously appearing on the internet, social networks and smartphone apps at an incredibly high rate[14]. The NPS market is diverse and dynamic, with the number of NPS rising from 166 by the end of 2009 to 950 substances detected by the end of 2019[13]. These new drugs are not subjected to clinical trials and information concerning toxicity and specific associated effects is still limited. Yet, animal and human studies showed that NPS are able to elicit not only rewarding and reinforcing effects [15][16][17][18], but also toxic effects of varying severity, at both the peripheral and central levels[19][20], despite an apparent, hazardous perception of safety[21]. Most of them are synthetic cannabinoids and cathinones, new hallucinogen and dissociative drugs or synthetic opioids, these latter representing a major source of social and clinical alarm, due to the numerous fatalities and intoxications associated with their use[22]. NPS represent a growing concern especially for mental health services[23][24], as they have been associated with the risk of violence in patients presenting to acute mental health services[25][26].

The use of NPS is widespread among adolescents, and a nationally representative study enrolling students in 8th to 12th grades across the US showed that boys are at greater risk for using synthetic cannabinoids and synthetic cathinones than girls[27]. Notably, NPS use is increasing in both male and female treatment-seeking opiate-dependent patients as a replacement to heroin and other opiates[28], due mostly to practical (e.g., greater availability) and economic rather than pharmacological factors[29]. There is also the possibility that female users may be at risk for being the experimental subjects of immoral drug dealers, i.e., to probe the effects of unknown, experimental synthetic drugs[30].

To date, knowledge of potential sex-dependent effects in the use and abuse of NPS is very scarce. Unfortunately, in many human and clinical studies involving subjects of both sexes, authors did not directly compare females to males, leaving the possibility of the existence of significant sex (animal studies) and gender (clinical studies) differences an open question.

The existence of a (still limited) number of differences in the behavioral and pharmaco-toxicological responses induced by NPS in male and female subjects. In general, the use of most NPS is prevalent among men than women. Preclinical studies, however, which allow greater control of individual variability (health status, taking other drugs, emotional conditions), have shown that females are more sensitive to the rewarding effects of synthetic cannabinoids and to the anxiety-related effects of synthetic cathinones than males (Table 1). Current knowledge on sex and gender differences in

NPS-induced effects is still inadequate, but the need for more studies is supported by the compelling evidence, showing important sex differences in the effects of their referent drugs (e.g., THC, cocaine, amphetamine, morphine). Similar to studies required for monitoring the pharmacological effects of therapeutic drugs, preclinical studies and clinical evaluations are needed to better understand the pharmaco-toxicological effects that NPS cause as a function of sex and gender. Such knowledge, in turn, will allow more effective, sex-tailored interventions to manage acute intoxications and reduce drug use.

Table 1. Summary of the evidence available so far describing sex-dependent differences or similarities in the prevalence of use and effects induced by new psychoactive substances (NPS) in males (M) and females (F). The symbol ? indicates the lack of data specifically comparing M vs. F. Abbreviations: 25I-NBOMe: dimethoxy-*N*-(2-methoxybenzyl)phenethylamine; α-PVP: α-pyrrolidinopentiophenone; CPP: conditioned place preference; DD: drug discrimination; IVSA: intravenous self-administration; KET: ketamine; MDPV: methylenedioxypyrovalerone; PPI: pre-pulse inhibition.

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	Scras	Synthetic Cathinones	Phenethylamines	Opioids
Prevalence of use (%)	**M > F [31]**	**M > F [32][33][34] M = F [35] (mephedrone)**	**M > F [36][37][38][39][40][1][41][42]**	**M > F [43][44] F > M [45][46] (prescribed drugs)**
Intoxications (%)	**M > F [31]**	**M > F [47]**	**?**	**M > F [43][44]**
Polydrug use	**M > F [48][49][50][51][52] (nicotine, alcohol, marijuana)**	**M > F [32][33] (alcohol, opioids)**	**?**	**?**
Age of 1st use	**M > F [53]**	**?**	**?**	**?**
Sensitivity to adverse effects	**M > F [54] (general side effects) F > M [55] (agitation, psychosis)**	**F > M [56] (anxiety, rats) M > F [57] (cardiovascular effects, rats) F > M [58] (tolerance to drug-induced hyperthermia, rats)**	**F > M [41] (2C-B, emotional verbal fluency) M > F [41] (2C-B, reduction in tiredness) F > M [42] (25I-NBOMe, hyperthermia) M > F [42] (25I-NBOMe, analgesia) M = F [42] (25I-NBOMe, PPI and visual sensorimotor responses)**	**?**
Sensitivity to rewarding effects (animals)	**F > M [59][60][61][62] (IVSA and DD)**	**M = F [63][64] (MDPV CPP and α-PVP IVSA) M > F [65] (α-PVP CPP)**	**?**	**F > M [66] (IVSA) M > F [[67] (food choice procedure)**

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