

EDITORIAL

New Psychoactive Substances (NPS), a New Global Issue: Neuropharmacological, Chemical and Toxicological Aspects

A rising global concern has been recently appeared on the new psychoactive substances (NPS) also referred to as legal highs, bath salts or research chemicals. Their pharmacological and subjective effects mimic those of “traditional” drugs of abuse but their legal state is often ahead of the law and sales channels are internet-bases. NPS belong to several chemical groups including but not limited to cathinones, tryptamines, phenethylamines, piperazines, piperidines, arylcyclohexylamines, synthetic cannabinoids, aminoindanes and arylalkylamines [1].

This thematic issue reviewed different aspects of most common plus emerging NPS: pattern of use and abuse, neuropharmacology, forensic and clinical toxicological issues and finally public concern that may create.

Special attention has been given to mephedrone, a designer drug structurally similar to cathinone, the main active constituent of the Khat plant (*Catha edulis*) [2].

Pantano and colleagues evaluated the emerging scientific literature on the possible mephedrone-induced neurotoxicity, focusing especially on the hypothesis of substance action on monoamine plasma membrane transporters for serotonin (5-hydroxytryptamine) and dopamine. Moreover, studies sustaining oxidative stress cytotoxicity and an increase in frontal cortex lipid peroxidation were also reported by the authors [3].

In order to document mephedrone abuse, taking into consideration the limitations of self-reports drug use, both for assessing the cause of the intoxication and for the evaluation of drug related impairment, Pascal Kintz illustrated the importance of mephedrone testing on hair in understanding the addiction pattern of the substance [4].

For its “entactogenic effects” mephedrone is mainly abused in nightclubs and parties but also in the context of “chemsex” a term coming from the contraction of “chemical sex”, coined to indicate the voluntary intake of certain psychoactive and non psychoactive drugs such as mephedrone itself but also, GHB, methamphetamine; crystal methamphetamine, erectile dysfunction agents, poppers in the context of sex parties and sexual intercourses with the intention of facilitating and/or enhancing the sexual encounter mostly among men who have sex with other men (MSM). Giorgetti *et al.* assessed the mechanisms of action, the toxicity and the pattern of use and abuse of substances involved in “chemsex” practice together with the sociocultural background and the health-related consequences that they may have on sexual behaviours in homosexual and bisexual users, including the risk of acquiring sexually transmitted infections [5].

Concerning not only sexual but also physical enhancing products, Pellegrini *et al.* showed the possible health hazards caused by the hidden presence of those pharmacologically active substances in physical and sexual performance enhancing products, which in recent the years have freely been sold mainly on internet web sites as dietary supplements [6].

Among biological matrices tested to verify the consumption of NPS, hair is the one with the widest time window of detection to investigate drug-related history and demonstrate past intake. Taking into account the growing number of rapid and sensitive methods for the determination of NPS in hair matrix which have been recently published, Kyriakou *et al.* overviewed the trends of the rapidly evolving analytical methods for the determination of NPS in hair and the usefulness of these methods when applied to real cases [7].

Maurer and his research group focused on two NPS, 3-methoxyphencyclidine (3-MeO-PCP) and 3-methoxyrolicyclidine (3-MeO-PCPy), which are derivatives of phencyclidine, an anesthetic pharmaceutical drug that was banned from the market in 1965 due to the high prevalence of dissociative hallucinogenic side effects. They elucidated the metabolic fate of these two NPS in rat and pooled human liver microsomes, the identification of the cytochrome P450 (CYP) isoenzymes involved and the detectability using standard urine screening approaches after intake of common users’ doses using gas chromatography-mass spectrometry (GC-MS), liquid chromatography-multi-stage mass spectrometry (LC-MSn), and liquid chromatography-high-resolution tandem mass spectrometry (LC-HR-MS/MS) [8].

Worthy of special attention are the range of evolutionary interpretations on the emerging subculture of the e-psychnauts and NPS reported by Orsolini *et al.* in the light of the fact that evolutionary research on drug abuse has previously been restricted to proximate studies, considering aetiology, mechanism and ontogeny. However, in order to explain the recent emergency of a new behavioural pattern (*e.g.* ‘the e-psychnaut style’) of NPS intake, a complementary evolutionary model may be needed and this manuscript addresses this issue [9].

Particularly original is the review proposed by Schifano, Pichini and their collaborators on neuropharmacology and psychoactive effects of the most used “herbal highs”: plant parts containing psychoactive substances. Most of the substances extracted from herbs, were originally used in the alternative ethnic medicine being at the centre of traditional commemorative rites since old centuries by ancient civilizations. Currently, these herbal products are mainly sold by internet web sites and easily obtained since some of them have no legal restriction. Nevertheless, for some of them evidences for an addiction potential with cognitive impairments suggest classification as a harmful drugs [10].

Finally, two valuable manuscripts have investigated synthetic cannabinoids (SCs), designer drugs not structurally but functionally similar to Δ^9 -tetrahydrocannabinol, the active principle of cannabis. SCs have generated an increasing public health concern since their introduction in the illicit drug market. Unlike Δ^9 -tetrahydrocannabinol, which is just a partial agonist of cannabinoid (CB) receptors, many SCs frequently act as full agonists on CB1 receptors and can cause unpredictable severe adverse effects even resulting

in death. Schaefer and colleagues studied the distribution of two selected SCs, namely 4-ethyl-naphthalen-1-yl-(1-pentylindol-3-yl)methanone (JWH-210) and 2-(4-methoxyphenyl)-1-(1-pentyl-indol-3-yl)methanone (RCS-4) in pigs [11], whereas Huestis and her research group have focused on N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide (ADB-FUBINACA) an emerging synthetic cannabinoid whose toxicological and metabolic data are currently unavailable. They determined optimal markers for identifying ADB-FUBINACA intake, moreover metabolic stability was also evaluated with human liver microsome incubations [12].

In conclusion, we hope that this Thematic issue will contribute to the advancement of knowledge currently available in the field of NPS and the global issue that they have generated since their appearance on the market.

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REFERENCES

- [1] Vaiano, F.; Busardò, F.P.; Palumbo, D.; Kyriakou, C.; Fioravanti, A.; Catalani, V.; Mari, F.; Bertol, E. A novel screening method for 64 new psychoactive substances and 5 amphetamines in blood by LC-MS/MS and application to real cases. *J. Pharm. Biomed. Anal.*, **2016**, *129*, 441-449. [<http://dx.doi.org/10.1016/j.jpba.2016.07.009>] [PMID: 27490334]
- [2] Busardò, F.P.; Kyriakou, C.; Tittarelli, R.; Mannocchi, G.; Pantano, F.; Santurro, A.; Zaami, S.; Baglio, G. Assessment of the stability of mephedrone in ante-mortem and post-mortem blood specimens. *Forensic Sci. Int.*, **2015**, *256*, 28-37. [<http://dx.doi.org/10.1016/j.forsciint.2015.07.021>] [PMID: 26295910]
- [3] Pantano, F.; Tittarelli, R.; Mannocchi, G.; Pacifici, R.; di Luca, A.; Busardò, F.P.; Marinelli, E. Neurotoxicity induced by mephedrone: An up-to-date review. *Curr. Neuropharmacol.*, **2017**, *15*, 738-749. [<http://dx.doi.org/10.2174/1570159X14666161130130718>] [PMID: 27908258]
- [4] Kintz, P. Evidence of 2 populations of mephedrone abusers by hair testing. Application to 4 forensic expertises. *Curr. Neuropharmacol.*, **2017**, *15*, 658-662. [<http://dx.doi.org/10.2174/1570159X14666161026152107>] [PMID: 27784226]
- [5] Giorgetti, R.; Tagliabracci, A.; Schifano, F.; Zaami, S.; Marinelli, E.; Busardò, F.P. When chems meet sex: a rising phenomenon called ChemSex. *Curr. Neuropharmacol.*, **2017**, *15*, 762-710. [PMID: 27855594]
- [6] Pellegrini, M.; Rotolo, M.C.; Busardò, F.P.; Pacifici, R.; Pichini, S. Non-allowed pharmacologically active substances in physical and sexual performance enhancing products. *Curr. Neuropharmacol.*, **2017**, *15*, 724-730. [<http://dx.doi.org/10.2174/1570159X14666161028125903>] [PMID: 27799033]
- [7] Kyriakou, C.; Pellegrini, M.; Garcia-Algar, O.; Marinelli, E.; Zaami, S. Recent trends in analytical methods to determine new psychoactive substances in hair. *Curr. Neuropharmacol.*, **2017**, *15*, 663-681. [<http://dx.doi.org/10.2174/1570159X156661611112545>] [PMID: 27834146]
- [8] Michely, J.A.; Manier, S.K.; Caspar, A.T.; Brandt, S.D.; Wallach, J.; Maurer, H.H. New psychoactive substances 3-methoxyphencyclidine (3-MeO-PCP) and 3-methoxyrolicyclidine (3-MeO-PCPy): metabolic fate elucidated with rat urine and human liver preparations and their detectability in urine by GC-MS, LC-(high resolution)-MSⁿ, and LC-high resolution-MS/MS. *Curr. Neuropharmacol.*, **2017**, *15*, 692-712. [<http://dx.doi.org/10.2174/1570159X14666161018151716>] [PMID: 27758707]
- [9] Orsolini, L.; St John-Smith, P.; McQueen, D.; Papanti, D.; Corkery, J.; Schifano, F. Evolutionary considerations on the emerging subculture of the e-psychoanalysts and the novel psychoactive substances: a comeback to the shamanism? *Curr. Neuropharmacol.*, **2017**, *15*, 731-737. [<http://dx.doi.org/10.2174/1570159X1566616111114838>] [PMID: 27834144]
- [10] Graziano, S.; Orsolini, L.; Rotolo, M.C.; Tittarelli, R.; Schifano, F.; Pichini, S. Herbal Highs: Review on psychoactive effects and neuropharmacology. *Curr. Neuropharmacol.*, **2017**, *15*, 750-761. [<http://dx.doi.org/10.2174/1570159X14666161031144427>] [PMID: 27799032]
- [11] Schaefer, N.; Kettner, M.; Laschke, M.W.; Schlote, J.; Ewald, A.H.; Menger, M.D.; Maurer, H.H.; Schmidt, P.H. Distribution of Synthetic cannabinoids JWH-210, RCS-4 and Δ^9 -Tetrahydrocannabinol After Intravenous Administration to Pigs. *Curr. Neuropharmacol.*, **2017**, *15*, 713-723. [<http://dx.doi.org/10.2174/1570159X1566616111114214>] [PMID: 27834143]
- [12] Carlier, J.; Diao, X.; Wohlfarth, A.; Scheidweiler, K.; Huestis, M.A. *In Vitro* Metabolite Profiling of ADB-FUBINACA, A New Synthetic Cannabinoid. *Curr. Neuropharmacol.*, **2017**, *15*, 682-691. [<http://dx.doi.org/10.2174/1570159X1566616108123419>] [PMID: 27829332].

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