

## Recent Changes in Drug Abuse Scenario: The New/Novel Psychoactive Substances (NPS) Phenomenon

**Fabrizio Schifano, MD, FRCPsych**

Over the last decade, the emergence of a vast range of new/novel/emerging psychoactive substances (NPS) has progressively changed the drug market scenario, which has shifted from a 'street' to a 'virtual'/online one.

Several definitions of NPS are in use, with the term 'new' not necessarily referring to new inventions but to substances that have recently been made available, possibly including a failed pharmaceutical or an old patent which has been 'rediscovered' as a 'recreational' molecule. Conversely, the term 'novel' can refer to something newly created; an old drug that has come back into fashion; or a known NPS molecule being used in an innovative or unusual way, hence presenting with a 'novelty' appeal (Corkery et al, 2018). Although misleading, the terms 'legal highs' or 'research chemicals' have been alternatively used to describe these molecules. NPS include synthetic cannabinoids, cathinone derivatives, psychedelic phenethylamines, novel stimulants, synthetic opioids, tryptamine derivatives, phencyclidine-like dissociatives, piperazines, GABA-A/B receptor agonists, a range of prescribed medications, psychoactive plants/herbs, and a large series of image- and performance-enhancing drugs (IPED) (Schifano et al, 2015). Overall, users are typically attracted by NPS due to curiosity and diffusion of social media users' experiences; easy availability/affordability from online drug shops; legality; intense psychoactive effects and likely lack of detection in routine drug screenings (Schifano et al, 2015).

Between 2004 and 2017, some 700-800 NPS were reported by the related European and international drug agencies (UNODC, 2018; EMCDDA, 2018), with most molecules identified being synthetic cannabinoids, synthetic cathinones, phenethylamine derivatives, and synthetic opioids. However, one could argue that the NPS scenario is much larger than that designed by those molecules which have been seized/formally identified by EU/international agencies. Since the online NPS scenario typically predicts the real life NPS scenario (Schifano et al, 2015), identifying what is being discussed online by the web-based NPS enthusiasts 'e-psychonauts' (Orsolini et al, 2015) may well be of interest. Consistent with this, a crawling/navigating software (i.e. the 'NPS.Finder®') was recently designed by our group. In November 2017, it has started to automatically scan, on a 24/7 basis, a vast range of psychonaut web fora for new/novel/emerging NPS. After a year of operation, it has been possible to estimate that the online/psychonaut web fora NPS scenario may include some 4,000 different molecules. Most popular NPS mentioned in the psychonauts' fora included: synthetic cannabimimetics; synthetic opioids; phenethylamines; designer benzodiazepines; and prescribed drugs.

The issue of NPS use, and especially so for synthetic cannabinoids and novel psychedelics, has been associated with a range of medical untoward consequences, including vomiting; seizures; cardiovascular complications; and kidney failure (Schifano et al, 2017). Conversely, main focus of this special issue is on the major psychopathological consequences of NPS use. Indeed, due to their complex pharmacodynamics, there are increasing levels of concern about the onset of acute/chronic psychopathological issues associated with NPS intake. The occurrence of psychosis has been related to: a) increased central dopamine levels, typically described with novel psychedelic phenethylamines, novel

stimulants and synthetic cathinones; b) significant cannabinoid CB<sub>1</sub> receptor activation, achieved with high potency synthetic cannabimimetics; c) 5-HT<sub>2A</sub> receptor activation, reported with latest generation phenethylamines, tryptamine derivatives and hallucinogenic plants; d) antagonist activity at n-methyl-D-aspartate/NMDA receptors, described with ketamine, methoxetamine/MXE, and their latest derivatives; and e) k-opioid receptor activation, typically associated with both *Salvia divinorum* and *Mitragyna speciosa*/'Kratom' intake.

Whilst considering the above, this Special Issue of Brain Sciences aims at providing an overview of a range of NPS-related issues. More precisely, Sahai et al present some original *preclinical data* relating in silico and in vitro assessment of psychoactive properties of a few dissociative diarylethylamines. Miolo et al focussed on specific *analytical chemistry* issues relating to amphetamine-type stimulants and ketamine, whilst Parrott argued about existing similarities between well-known recreational drugs and NPS in terms of *mood fluctuations/psychobiological instability issues*. Conversely, Cohen and Weinstein presented original *cognitive psychopharmacology* data relating to the use of organic and synthetic cannabinoids. From the *clinical point of view*, Bonaccorso et al presented a case series of synthetic cannabinoid users presenting to acute psychiatric services with psychosis; Frisoni et al commented on the medical consequences of novel opioids' intake; Martinotti et al provided a thorough overview of the hallucinogen-persisting perceptual disorder, an issue of clear interest for NPS users; Schifano et al commented on the misuse/abuse of prescribed medicines (e.g. benzodiazepine derivatives; methylphenidate look-alikes; and fentanyl analogues) in the NPS scenario context; and, finally, Gittins et al provided empirical data relating the NPS use in clients seeking treatment in the UK. Both Wadsworth et al and Miliano et al commented extensively on the *role of the open/deep web* in shaping and promoting changes in NPS scenario. Finally, both Metastasio et al and Catalani et al presented original data shedding further light on the expanding phenomenon of *IPED misuse/abuse*.

In parallel with constant changes in basic structures from which emerging molecules can be derived/designed/synthesized, the NPS market will continue to expand. This will pose a challenge, since NPS-related toxidromes are, per se, complex and unpredictable, and clinicians should aim at being better educated in recognizing NPS-related toxicity issues. Drug control policies should be improved worldwide, and the list of NPS should be constantly updated with improvement in analytical chemistry detection methods. Given the implication on mental health, psychiatric services should adapt to the new drug scenarios whilst drafting new treatment strategies.

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