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The clinical challenges of synthetic cathinones

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Aims: Within the new psychoactive substances (NPS) scenario, several hundred different molecules, mostly including synthetic cannabinoids and cathinones, have been identified so far. The aims of the paper were to: (i) identify the number of synthetic cathinones mentioned in a range of psychonaut, NPS-related, online sources; and (ii) describe the associated acute/long term clinical scenario and the related treatment/management plan.

Methods: After about 18 months of operation and exclusion of false positives/duplicates, some 4204 unique NPS molecules were included in the NPSfinder® crawling/navigating software database. Most popular NPS included: 1265 psychedelic phenethylamines (30.1%; confidence interval [CI] 95%: 28.7–31.5%); 1253 synthetic cannabinoids (29.8%; CI 95%: 28.4–31.2%); 429 synthetic opioids (10.2%; CI 95%: 9.3–10.2%); and 171 synthetic cathinones (4.1%; CI 95% 3.5–4.7%). Conversely, the United Nations Office on Drugs and Crime and the European Monitoring Centre for Drugs and Drug Addiction databases respectively included 169 and 140 cathinones. Overall, the 3 databases reported some 222 synthetic cathinones, and 41 were uniquely identified by the NPSfinder®.

Results: In terms of clinical scenarios, synthetic cathinone ingestion is initially associated with stimulant effects; however, psychopathological disturbances, violence, suicidal behaviour, hyperthermia, coma and death have also been described.

Conclusion: The proportion of cathinones commented on by psychonaut fora appeared to be relatively small, and similar to those reported by both the United Nations Office on Drugs and Crime and European Monitoring Centre for Drugs and Drug Addiction. This may be associated with a recent significant decline in both cathinone-related consumption and acute medical presentation. Due to their complex behavioural and medical toxicity issues, healthcare professionals should be, however, be educated to recognise the signs and symptoms of NPS, including synthetic cathinone, ingestion.

KEYWORDS

drug misuse, drug prevention, new psychoactive substances, synthetic cathinones, drug-induced aggression

The authors confirm that the Principal Investigator for this paper is Fabrizio Schifano and that he had direct responsibility for the drafting of this paper; no direct contact or clinical care activities were conducted relating to the current project

1 | INTRODUCTION

Among new psychoactive substances (NPS), cathinones constitute a very relevant group to clinicians, policy-makers and other stakeholders.[1] Mephedrone was reportedly first synthesized in 1929.[2] In 2007, reports of 4-methylmethcathinone (mephedrone) use emerged, first in Israel and then in other countries and regions, including Australia, Scandinavia, Ireland and the UK.[3] In 2008, it was first reported to the European Early Warning System by the UK and by Finland, after being associated with adverse health effects.[4] Cathinones are β-keto derivatives of phenylethylamines/amphetamines which are actively being subjected to minor modifications at the alkyl chains or the aromatic ring to create new synthetic molecules with the goal of circumventing laws.[5] Synthetic cathinones are usually insufflated or swallowed in their powder or crystal forms but can also be administered by injection, smoking, mucosal delivery or injection via intramuscular or other routes.[6]

1.1 | Clinical neuropharmacological issues

Cathinones are typically categorised based on either their pharmacological action or properties,[5,7] or in comparison to *traditional* stimulant drugs (for a review of the issue, see[8]). Some classifications consider their effects in relation to different substrates or non-substrate transporter inhibitors.[9] Four categories of synthetic cathinones are typically described in terms of their behavioural effects (for a thorough review, see[10] and[1]):

- Cocaine/3,4-methylenedioxymethamphetamine (MDMA)-related effects; these are reported with a range of molecules including: mephedrone, 4-methylethcathinone (4-MEC), methylone, ethylone, butylone and naphyrone are substrates for the dopamine (DA) transporter (DAT), norepinephrine (NE) transporter, and serotonin transporter (SERT)[10];
- MDMA-related effects; associated with: methedrone and 4-trifluoromethylmethcathinone exhibit a higher inhibitory potency at SERT compared to their DAT activity, but at the same time promote release of both NE and 5-HT, like amphetamine analogues such as MDMA, paramethoxymethamphetamine (PMMA), paramethoxyamphetamine (PMA) and 4-ethylthioamphetamine (4-MTA)[11,12];
- Methamphetamine-like effects; associated with: cathinone, methcathinone, flephedrone, ethcathinone and 3-fluoromethcathinone are monoamine transporter substrates with DAT selective profiles; they show high inhibitory potencies at DAT and exhibit lower inhibitory potencies at SERT.[9,12] They promote the release of NE and DA in a similar way to methylamphetamine[10];
- Pyrovalerone-like effects; associated with: pyrovalerone, methylenedioxypyrovalerone (MDPV) and α-pyrrolidinovalerophenone (α-PVP). They are non-substrate transporter inhibitors, showing inhibitory potencies at NE transporter and DAT ≥ methylamphetamine[13] or cocaine.[14,15] MDPV and α-PVP are both considered to be cocaine-like, whilst being more effective reinforcers.[16] Recent research on the pyrovalerone analogue α-pyrrolidinopentiothiophenone (α-PVT) suggests it has reinforcing and rewarding effects similar to those of both methylamphetamine and cocaine.[17]

It has been suggested that the reinforcing properties of cathinone stimulants are positively correlated with their selectivity for the dopamine (DAT) relative to SERT.[15,18-20]

What is already known about this subject

- Four categories of synthetic cathinones are typically described, e.g. those possessing: cocaine/3,4-methylenedioxymethamphetamine-related effects (e.g. mephedrone); 3,4-methylenedioxymethamphetamine-like effects (e.g. methedrone); methamphetamine-like effects (e.g. cathinone); and pyrovalerone-like effects (e.g. methylenedioxypyrovalerone).
- By April 2019, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) database had 749 new psychoactive substance entries, whilst the latest United Nations Office for Drugs and Crime (UNODC) listed a total of 964 substances on their NPS database, with most molecules identified being synthetic cannabinoids and synthetic cathinones.
- It could be argued that the NPS total may be higher in number than those described by both the UNODC and the EMCDDA, with e-psychonaut-NPS discussions typically predicting the real life NPS scenario.

What this study adds

- With the help of an *ad hoc* crawling/navigating software (NPSfinder®), designed to automatically scan the open/surface web, some 4204 unique NPS molecules were identified, with 171 (4.1%; confidence interval 95% 3.5–4.7%) being synthetic cathinones.
- NPSfinder® has identified some 41 cathinone molecules not known to either the UNODC or EMCDDA.
- Clinical ill-health consequences of taking cathinones may be wholly consistent with their neuropsychopharmacological characteristics. Initial stimulant effects are associated with a range of acute psychiatric disturbances, including violence/aggression and suicidal thoughts, together with hyperthermia, coma, and death.
- NPS, including synthetic cathinones, represent a challenge to healthcare, with complications of their use and their impact on services still being relatively unknown.

Overall, synthetic cathinone pharmacokinetics can be somewhat predicted considering the modifications made to the core scaffold.[21] When ingested, the metabolic disposition of mephedrone in preclinical models is characterized by low bioavailability and an extensive hepatic metabolism.[22] Its metabolism has been well described in rats.[23] In humans, Olesti et al.[24] carried out a randomized, crossover, phase I clinical trial. Subjects received 50 and 100 mg (n = 3) and 150 and 200 mg (n = 6) of mephedrone. Mephedrone peak concentrations were reached in 1 h, with peak plasma concentrations and the amount of drug recovered in urine increasing with the doses administered, suggesting that mephedrone presented with a linear dose-dependence. Mephedrone presented a similar elimination constant rate (Ke; at ~0.3/h) and elimination half-life ($t_{1/2}$ of ~2 h), irrespective of the administered dose. Mephedrone and methylone are chemically alike; conversely, MDPV presents with lower time to maximum concentration and $t_{1/2}$ levels and pentylone shows longer $t_{1/2}$ (for a thorough review of the issue, see[20]). Several phase I metabolites retain pharmacodynamic activity; CYP2D6 is implicated in the metabolism of all synthetic cathinones, and this implies that recreational users with no or low CYP2D6 functionality are exposed to unwanted acute toxicity episodes.[24]

Up to 30% of mephedrone users may report dependence,[25] with synthetic cathinone users possibly experiencing as well both tolerance and withdrawal symptoms,[26] which include tiredness, insomnia, nasal congestion and impaired concentration.[27] Cathinone addicts commonly report re-injecting of the drug with excessive binge use over long periods of time, with shorter half-life and duration of effects leading to more compulsive drug-taking behaviour to maintain euphoria.[28]

1.2 | Number and types of NPS and synthetic cathinones in both real and online scenarios

By April 2019, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) European Database on New Drugs database had 749 entries, whilst the latest United Nations Office on Drugs and Crime (UNODC) listed a total of 964 substances on their NPS database.[29-32] Most molecules identified include synthetic cannabinoids and synthetic cathinones. However, it could be argued that the NPS scenario is much larger than that outlined by those molecules which have been seized and formally identified by both the UNODC and the EMCDDA. Since the *online* NPS scenario typically predicts the *real-life* NPS scenario,[6,33] identifying what is being discussed online by web-based NPS enthusiasts, or *e-psychonauts*,[34,35] may well be of interest.

1.3 | Aims

The aim of the paper was to: (i) identify and describe the number of synthetic cathinones available as identified from a range of psychonaut, NPS-related, online sources; and (ii) describe both the acute/long term clinical scenarios associated with synthetic cathinone intake and the possible treatment/management plan to best cope with the medical and psychopathological associated ill-health consequences.

2 | MATERIALS AND METHODS

To facilitate the process of early recognition of the increasing dissemination of new substances online and the variability of information sources, a crawling/navigating software (i.e. the *NPSfinder*®) was designed to automatically scan the *open/surface web* for new/novel/emerging NPS.[36] This was designed to map on a 24/7 basis the large variety of psychoactive molecules mentioned/discussed within a range of major and representative online psychonaut websites/fora.

The NPSfinder® was designed by Damicom, an IT enterprise based in Rome (Italy), to extract a range of information regarding NPS, including: chemical and street names; chemical formula; 3-dimensional image; and anecdotally reported clinical/psychoactive effects. Resulting data were checked against the EMCDDA and UNODC NPS databases. The collection of further information was completed by consulting a range of open libraries and chemistry databases referring to the index item, if existing. These data were then automatically stored in an online, restricted access/password-controlled database located within firewall protected, highly secure and consistently performing servers. A number of proper piloting searches were first carried out; with the help of most common search engines, including Google, the informatics' staff started navigating using a range of keywords, including: NPS; novel psychoactive substances; new psychoactive substances; emerging psychoactive substances; drugs online; buy new substances; psychonauts, drug forums; psychoactive products; synthetic cannabinoids; synthetic cathinones; psychedelic phenethylamines; novel stimulants; synthetic opioids; tryptamine derivatives; phencyclidine-like dissociatives; piperazines; GABA-A/GABA-B receptor agonists; prescribed medications; psychoactive plants; psychoactive herbs; and image- and performance-enhancing drugs. Any new website of interest was added to the list, whose final version is attached as Appendix 1. Although the language most typically used in these websites was English, further languages here analysed by NPSfinder® included: Dutch, French, Turkish, Swedish, Spanish, German, Russian and Italian.

Afterwards, a range of specific web scraper/crawler activities, to extract all accessible posts/entries from 26 November 2017 to 31 May 2019, were carried out. Data were captured with the help of a range of Python language web crawlers, 1 for each font, through daily scanning activities. Emerging data were then imported and stored in a MYSQL database, which presented with an SSL security protocol. All data were encrypted with asymmetric cryptographic procedures. Data were first stored in an intermediate virtual storage area. Eventually, with the help an *ad-hoc* check control panel, all data were manually and carefully analysed by 4 medically/psychiatrically-trained professionals (F.N., D.A., C.Z. and L.G.). In case of data interpretation

issues, these were resolved with the help of F.S. and A.V. In this way, a full assessment and editing of each NPSfinder® data entry was carried out and the range of unique synthetic cathinone molecules here commented were identified.

When any new item was detected during the automated web scan, the system sent an e-mail notification/alert to the core researchers' mailing list. Eventually, these data were screened for both relevance and to exclude possible duplications. Finally, using chemical structure identification and published related data, researchers assigned each molecule to its NPS drug class, consistent with Schifano et al.[6]

To describe the medical and psychopathological issues most typically associated with the range of synthetic cathinone intake, the Medline/PubMed database(s) were searched for papers using the following keywords alone or in combination: 'new psychoactive substances', 'novel psychoactive substances', 'synthetic cathinones', 'medical consequences', 'psychopathological consequences', 'psychiatric consequences', and 'treatment and management of acute toxicity', 'clinical consequences', 'mephedrone', '4-methylethcathinone (4-MEC)', 'methylone', 'ethylone', 'butylone', 'naphyrone', 'methedrone', '4-trifluoromethylmethcathinone', 'methcathinone', 'flephedrone', 'ethcathinone', '3-fluoromethcathinone', 'pyrovalerone', 'MDPV', 'alpha-pyrrolidinovalerophenone (α-PVP)', and 'pyrrolidinopentiothiophenone (α-PVT)'.

In assessing the abstracts that were identified by the search, the papers of interest were narrowed down to focus on human reports only; the description of both acute/chronic toxicity and dependence potential were also included.

2.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

Data from the NPSfinder® *web crawling activities*

After about 18 months of operation, the number of substances identified by the web crawler activities was 5922. By the time of writing, some 4204 unique NPS molecules were included in the database and 1718/5922 (29.01%) remaining molecules were designated as false positives/duplicates. Most popular NPS mentioned in the psychonaut fora included: 1265 psychedelic phenethylamines (30.1%; confidence interval [CI] 95%: 28.7–31.5%); 1253 synthetic cannabinoids (29.8%; CI 95%: 28.4–31.2%); 429 synthetic opioids (10.2%; CI 95%: 9.3–11.1%); and 171 synthetic cathinones (4.1%; CI 95% 3.5–4.7%; see list in Appendix 2). Conversely, by the end of May 2019 the UNODC listed some 169 synthetic cathinones and, by 1 April 2019, the EMCDDA database included 140 different synthetic cathinones. Overall, the 3 databases identified some 222 synthetic cathinones. More precisely, some 121 cathinones were common to the 3 databases; 41 were uniquely identified by the NPSfinder®; 37 were identified only by the UNODC and 7 only by the EMCDDA (for more details, see Appendix 2).

Synthetic cathinone-related clinical issues; drafting a rational treatment and management plan

The search conducted for this study identified 40 papers focussing on either synthetic cathinone medical/psychopathological consequences and/or their treatment/management approach(es).

Clinical ill-health consequences following consumption of synthetic cathinones are overall consistent with their neuropsychopharmacological characteristics. After intake, initial stimulant effects e.g. euphoria, improved psychomotor speed, alertness and talkativeness[37] are typically observed. Acute psychiatric effects may, however, also include: low mood, loss of appetite, difficulty sleeping, a degree of paranoid ideation, cognitive impairment, changes in perception, agitation, hallucinations, delusions, amnesia, confusion, violence, suicidal thoughts[37,38] and excited delirium.[39] With synthetic cathinones, suicides by hanging and deaths from firearm injuries have frequently been reported.[40-42]

Like amphetamine, synthetic cathinones result in medical side-effects consistent with sympathomimetic toxicity.[43-45] Hence, acute intoxication issues include hypertension, tachycardia, cardiac, kidney and liver failure, rhabdomyolysis, electrolyte imbalance, metabolic toxicity, paradoxical hypoglycaemia,[46] and cerebral oedema.[47-49] Flushing, sweating, chills, restlessness, shortness of breath, dry mouth, abdominal pain, anorexia, vomiting, erectile dysfunction and discolouration of the skin have also been reported.[6] Le Roux et al.[50] analysed some 105 amphetamine-like (including synthetic cathinones; 10% of the total) drug poisoning cases. The most frequently reported symptoms included anxiety and hallucinations (49%), mydriasis and headache (41%), tachycardia (40%), and hypertension (15%). Complications such as seizures (7%), cardiac arrest (5%), toxic myocarditis (1%) and haemorrhagic stroke (1%) were also observed. Cathinone-induced acute intoxication may be characterized as well by symptoms/signs of the serotonin syndrome, which is associated with hyperthermia, psychotic disorders, catatonia and hyperactive delirium.[51,52]

Synthetic cathinone fatalities[8,53] are typically attributed to hyperthermia,[54,55] hypertension, cardiac arrest and more in general to the classic serotonin syndrome.[56,57] Only rarely was the concentration of the parent drug causing fatality higher than 1 mg/L in postmortem biological fluids.[57] Ezaki et al.[58] compared data relating to victims from either 12 synthetic cathinone or cannabinoid intake and 10 methamphetamine cases. Whilst acute intoxication and cardiac ischaemia were the 2 most prominent causes of death in both synthetic cathinone/cannabinoid users and methamphetamine users, excited delirium syndrome, pulmonary aspiration and drowning were found only in synthetic cathinone/cannabinoid cases. Synthetic cathinone use alone is rare and the use of multiple substances may facilitate the occurrence of adverse effects, especially in females (for a review of the issue, see[59]). Of particular concern may be the significant enhanced

effect on central DA levels of MDPV, mephedrone and methylone taken in combination.[60]

Once the initial phase of ingestion is over and the patient is medically stabilized, there may be a potential risk for long-term psychiatric problems.[60,62] Furthermore, synthetic cathinones appear to induce neurocognitive dysfunction and cytotoxicity, which are dependent on drug type, dose, frequency and time following exposure.[63] Also, orodental adverse effects, consistent with those observed with amphetamine, have been associated with a chronic exposure to synthetic cathinones.[64] Finally, the intravenous administration of synthetic cathinones, which is not limited to the context of either the 'chemsex'[65] or the 'slamming'[43] scenarios, has been related to a range of behavioural problems.[66]

3.1 | Cathinone categories; clinical peculiarities

Taking into account cathinone's pharmacological[9] and behavioural effects' classification described above,[1] a few differences seem to emerge between the different categories.

Considering the cocaine/MDMA-mixed effect molecules such as mephedrone and related compounds, mephedrone has been the most investigated.[67,68] Furthermore, Roberts et al.[45] found that mexedrone, a mephedrone derivative, was found in 11 of 305 patients who presented to an emergency department (ED). All of them presented with agitation and 6 patients required sedation and/or physical restraint. Conversely, Karila et al.[68] emphasized that the potential chronic health effects (e.g. reproduction toxicity, genotoxicity and carcinogenic potential) of mephedrone/methylone prolonged use remain to date unknown.

No specific clinical concerns have been described for *MDMA-like effects' molecules* such as methedrone and 4-trifluoromethylmethcathinone. Conversely, in association with the misuse of *methamphetamine-like cathinones*, both Iqbal et al.[69] and Fudalej et al.[70] have highlighted the risk of manganese poisoning with Parkinsonism features reported in European clients who had injected self-prepared methcathinone hydrochloride (ephedrone) synthesized from pseudoephedrine hydrochloride using potassium permanganate as a potent oxidant.

Finally, increasing levels of clinical concerns have been associated with the use of *pyrovalerone-like molecules*, including α-PVP and MDPV, whose clinical effects are individual, dose- and route of administration-dependent.[71] Palamar et al.[72] analysed data from a 2016/2017 large-scale (n = 3786) US study of high school senior subjects. Overall, 0.8% (95% CI: 0.5–1.2) of seniors was estimated to have used α-PVP (*flakka*; *zombie drug*) over the previous year. Flakka users reported high prevalence of use of other drugs, particularly synthetic cannabinoids (85.6%), ketamine (72.3%), marijuana (59.1%) and γ-hydroxybutyrate (47.5%). With α-PVP, a range of exaggerated symptoms, such as feelings of incredible strength, disorientation, aggression and altered thought processes, together with high liability for abuse, tachycardia, agitation, hypertension, hallucinations, delirium, mydriasis, hyperthermia and coma, have been reported.[62,73] Umebachi et al.[74] described a retrospective case series including 8 subjects who had visited the local hospital ED between March 2012 and November 2014 and had analytically confirmed blood α-PVP levels. Drug preparations had been administered by rectal insertion or inhalation; the time interval between drug intake and ED presentation was 8.5 (1–24) h, with blood α-PVP concentrations ranging from 1.0 to 52.5 ng/mL. Symptoms of high body temperature (3/8), tachycardia (5/8), hypertension (3/8), acid-base balance disorder (5/8), coagulopathy (4/6), increased blood creatinine phosphokinase (6/8) and blood lactate levels (5/7) were observed. Use of flakka has been associated with at least 80 deaths in the USA.[72] In a forensic setting, MDPV was detected in blood and urine samples of 50 individuals involved in violent crimes, including bodily harm, robberies, homicides and acts of resistance. In many cases, subjects showed highly aggressive and violent behaviour; the risk for such behaviours increased with MDPV plasma concentrations above 30 mg/L.[75] According to Szily and Bitter,[76] in Hungary there has been an increasing number of hospitalized patients with acute psychosis using MDPV. Finally, Dzhuvalyakov et al.[77] collected postmortem samples taken from 13 pyrrolidinovalerophenone poisoning victims from the Astrakhan region; they identified signs of chronic intoxication, which manifested themselves in the form of mixed gliosis and various lesions of brain neurons.

3.2 | Cathinone intake: treatment/management plan

It is problematic to draft a universally valid treatment/management plan to cope with the medical, behavioural and psychopathological disturbances related to the intake of the virtually several hundred synthetic cathinones here identified, often taken in combination with other traditional and NPS[78] currently available. Furthermore, it has been suggested that signs, symptoms, and treatment of toxicity with synthetic cathinones, synthetic cannabinoids, or dextromethorphan may overlap significantly.[79,80] Consumers of synthetic cathinones may present to EDs without providing information about the substances(s) ingested; standard drug tests will show negative results; and sophisticated tests are not carried out as part of typical clinical practice.[81] Furthermore, neither gas chromatography–mass spectrometry nor gas chromatography–Fourier-transform infrared spectroscopy alone can successfully differentiate between all synthetic cathinones.[82]

Some clients may simply need reassurance, support and medical monitoring. Management of cathinone, and indeed of any NPS/unknown psychotropics' ingestion, is typically directed at dealing with adverse effects as they arise.[83] Due to the similarity of cathinones with other stimulants, management strategies similar to those recommended for intoxication with those drugs might be useful.[84] For example, if a diagnosis of cathinone-induced delirium is suspected, treatment efforts should focus on controlling agitation and then treating medical complications such as metabolic acidosis.[43] Symptom-directed supportive care may also include the management of convulsions, hypertension/hypotension and rhabdomyolysis.

Treatment of the cathinone-associated serotonin syndrome, which is often associated with agitation, may be managed using both benzodiazepines and cyproheptadine.[81] The observation of asymptomatic patients should continue for a few hours (for a review, see also[83]).

When medication is needed, given the cathinone complex/unknown pharmacology, benzodiazepines may be the agents of choice. Agitated adults can be sedated with an initial dose of oral or intravenous **diazepam** (0.1–0.3 mg/kg body weight). At times, larger doses/frequent re-dosing to achieve adequate sedative effect may be required.[83,85] Further targeted treatment to control aggression and agitation may include intramuscular or intranasal **midazolam**, or intramuscular **lorazepam**. This approach may be useful as well to stop seizures.[1] Benzodiazepines, however, may be a problem whilst in presence of alcohol and, where patients cannot be controlled with benzodiazepines alone, propofol and/or antipsychotics may be considered. However, drugs such as **haloperidol**, **olanzapine** or **ziprasidone** can lower seizure thresholds, and contribute to dysrhythmias.[81] In general, the use of atypical antipsychotics including the psychonauts' *ideal trip terminator*[86] olanzapine, has shown good efficacy in containing episodes of aggression in different cohort and different phases of illness.[87] Finally, treatment for patients with prolonged exposure to synthetic cathinones should ideally include a drug management plan coupled with psychotherapy.[68]

4 | DISCUSSION

The present paper provides unique, unprecedented, figures in terms of overall numbers of synthetic cathinones; it presents as well with an overview of the ill-health effects associated with the ingestion of these compounds, which are intended to mimic the effects of traditional stimulants.

The number of synthetic cathinones here identified with NPSfinder® was comparable with that identified by the UNODC, and higher than that listed in the EMCDDA database. Out of the 222 synthetic cathinones overall identified by the 3 databases, NPSfinder® captured 171/222 (77%) of them, a performance figure very similar to the UNODC database (169/222; 76%), but better than the EMCDDA (140/222; 63%). One could argue that these differences may be due to the EMCDDA focusing on 28 EU countries only, whilst both the UNODC database and the psychonaut entries may better reflect the global situation.

Conversely, in comparison with remaining approaches, one would have hypothesized with the NPS.Finder approach the mention by psychonauts of a much larger number of synthetic cathinones. In fact, if one considers the whole number of molecules identified through analysis of data based on psychonauts' discussions, the NPS.Finder database has identified a quantitative level of NPS that is about 5-fold higher than those mentioned by both the UNODC and the EMCDDA.[35] It is of interest to note, however, that synthetic cathinones accounted here for only 4.1% of the whole number of web crawler database molecules. This is in sharp contrast with UNODC data, where synthetic cathinones are second only to synthetic cannabinoids/*spice* in terms of number of NPS seized over the years.[89] Similarly, synthetic cathinones were the NPS most seized in 2016 in the EU.[90] By contrast, psychonauts may well focus their discussions, more than anything else, on those issues that are topical.[35] Consistent with this, it is of interest to note that Webb et al.[90] found that cathinone-related presentations to UK EDs, over the last couple of years, significantly declined in number. Furthermore, the England and Wales 2017 survey data showed that last year mephedrone use among 16- to 34-year-olds was estimated at 0.2%, down from 1.1% in 2014/15.[30] This is echoed by a fall in the number and quantity of mephedrone seizures by UK law enforcement agencies,[90,92-94] as well as those presenting for treatment for mephedrone in England,[95,96] and those whose deaths involved mephedrone.[8] In other words, there might have been a recent decline in interest towards synthetic cathinones, and one could wonder if this is linked to increased availability of higher purity/high dose MDMA/psychedelic phenethylamine products.[30] One could also argue that the market has reached a point of saturation for molecules being offered to synthetic cathinone enthusiasts.

From the present overview, it seems that together with the vast range of NPS, synthetic cathinones represent a clinical challenge, with complications of their use and their impact on services still being relatively unknown.[97] Indeed, synthetic cathinone intake is typically associated with an imbalance of a range of neurotransmitter pathways/receptors, and consequently with a significant risk of both medical and psychopathological disturbances, at times accompanied by bizarre behaviour and significant violence/aggression levels.[6] A paucity of information exists on the biological, physiological and toxicological effects of synthetic cathinones, especially regarding their long-term effects after heavy and prolonged use. It is paramount that healthcare professionals are able to recognize the signs and symptoms of synthetic cathinone ingestion, know the steps to take to ensure safety of the patient and those around them.[62]

Vulnerable subjects, including children/adolescents and psychiatric patients, may be exposed to large number of pro-drug web pages, from which anecdotal levels of knowledge related to both well-known and novel psychotropics are typically provided by e-psychonauts (e.g. drug fora/blog communities' members). Hence, future approaches should consider the role of web-based preventative strategies in targeting youngsters/vulnerable individuals at risk of approaching the drug market.

4.1 | Limitations

It has to be emphasized here that the NPS.Finder crawled so far on the open web only. Since there may well be further information available on both the deep web and the dark net, future studies of our group will be focussing on expanding drug searches on these less accessible areas of the web. NPS.Finder-based studies will need to focus as well on further languages, which should include: Chinese, Japanese and Arabic, since previous studies have highlighted their importance in NPS-based studies.[98] Furthermore, from a formal point

of view the current literature review would not be considered as *systematic*. Instead, it was conceived as a literature overview, focussing on the cathinone clinical issues of interest.

5 | CONCLUSIONS

More studies should aim at providing better levels of misusing drugs' clinical pharmacological-related knowledge, so that properly tailored management/treatment strategies and guidelines can be drawn up and made available.

Because of the complex behavioural and medical toxicity issues, raising awareness of and education on drugs' health harms, interventions, harm reduction techniques, and referral pathways are here considered to be of relevance for healthcare professionals.[1,99]

COMPETING INTERESTS

The authors have no conflicts of interest to declare.

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CONTRIBUTORS

F.S. and A.V. conceived the idea of the manuscript and coordinated the whole project. F.N., C.Z., D.A. and L.G. carried out the process of both data collection and systematisation. A.G. and J.M.C. contributed to the literature overview, provided relevant epidemiological data and contributed to the drafting of the paper itself.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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