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Review Article

New trends of drug abuse in custodial settings: A systematic review on the misuse of over-the-counter drugs, prescription-only-medications, and new psychoactive substances

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ABSTRACT

The article presents a systematic literature review on the use and the psychiatric implications of over-the-counter drugs (OTC), prescription-only-medications (POM), and new psychoactive substances (NPS) within custodial settings. The searches wer carried out on 2 November 2022 on PubMed, Scopus, and Web of Science in line with PRISMA guidelines. A total of 538 records were identified, of which 37 met the inclusion criteria. Findings showed the most prevalent NPS and OTC and POM classes reported in prisons were synthetic cannabinoids receptor agonists (SCRAs) and opioids, respectively. NPS markets were shown to be in constant evolution following the pace of legislations aimed to reduce their spread. The use of such substances heavily impacts the conditions and rehabilitation of persons in custody, with consequent physical and mental health risks. It is important to raise awareness of the use and misuse of such substances in prisons (i) from an early warning perspective for law enforcement and policy makers (ii) to prompt doctors to cautiously prescribe substances that may be misused (iii) to improve and increase access to treatment provided (iv) to add such substances to routine toxicological screening procedures (v) to improve harm reduction programmes.

1. Introduction

Over the last twenty years, drug use has changed radically due to the advent of the Internet, which has influenced the use and market of substances. This has led to the appearance and spread of a large number of molecules latterly termed 'new psychoactive substances' (NPS) (Schifano et al., 2018). For instance, dentification of NPS by authorities worldwide has surged by over 400 % since 2009. By the end of 2019, a total of 950 new substances had been detected globally, with 790 already available in the European market, as reported by the EU Early Warning System (UNODC, 2019; EMCDDA, 2020). The United Nation Office on Drugs and Crime (UNODC) and the European Monitoring Centre on Drugs and Drugs Abuse (EMCDDA) defined NPS as 'substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat' (EMCDDA, 2018; UNODC, 2021). These are characterized by presentations of acute drug toxicity, unknown effects, poor safety profiles, and psychiatric consequences (Miliano et al., 2018; Schifano et al., 2017, 2018, 2021). While the profound psychiatric implications of

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traditional substances of misuse, such as cognitive impairment potentially progressing to neurocognitive disorders (Verdejo-Garcia et al., 2019), the association with affective disorders (Tolliver and Anton, 2015) or induced psychosis/psychotic onset (Martinotti et al., 2021), the link with impulsivity and risky behaviours (Mosca et al., 2023), as well as dependence and withdrawal (Hasin et al., 2013) are well-recognized, the risks associated with NPS use for mental health are not yet fully understood and may indeed entail even more severe psychopathological consequences (Chiappini et al., 2021). NPS include stimulants, synthetic cannabinoids receptor agonists (SCRAs), opioids, benzodiazepines and other sedative-hypnotics, hallucinogens, and dissociatives. Many of these substances are intended to mimic the effects of internationally controlled drugs and are sold as 'legal' substitutes of or alternative to traditional drugs of abuse/misuse (EMCDDA, 2022). However, over the years to follow, these substances became regulated by individual countries, which have been applying ad-hoc legislation to limit their diffusion. For instance, in the United Kingdom (UK), the 'Psychoactive Substances Act' (PSA) came into force in 2016; this was a blanket-ban making illegal supply or offer to supply, produce, import/export, possess with the intention to supply of any substance with a psychoactive effect (GOV.UK, 2016). The PSA also made illegal and punished the possession of such substances within prisons, to try and limit the spread of such substances in this marginalised sub-population. As the consumption of conventional substances of misuse continued, there was a gradual emergence of improper use and misuse of over-the-counter (OTC) medicines, available without a prescription and sold under the supervision of a pharmacist, as well as prescription-only medications (POM). This misuse was driven by the desire to achieve psychoactive effects (Schifano et al., 2021). By 'misuse' of OTC/POM, we have previously suggested that this refers to the use of pharmaceutical outside the prescribing guidelines or licensing, involving the use of high or super-high dosages or through unusual routes of administration (Schifano et al., 2018), including intravenous and intranasal intake modalities. This phenomenon had already been widely described and documented in the general population and defined as 'pharming' (Chiappini and Schifano, 2020; Levine, 2007). Since 2006, OTC and POM were reported to be used in much the same way also in prisons. Pharmaceuticals misused include some antidepressants, e.g., bupropion (Reeves and Ladner, 2013; Schifano and Chiappini, 2018), sertraline and amitriptyline (McKendy et al., 2021); certain antipsychotics e.g., quetiapine and olanzapine (Chiappini and Schifano, 2018); some antiepileptics such as the gabapentinoids (Deeb et al., 2020), phenytoin, carbamazepine, divalproex (McKendy et al., 2021); several opioids e.g., buprenorphine (Rao et al., 2016), codeine (Paterson and Cordero, 2006), fentanyl (Bucerius and Haggerty, 2019), morphine (Postigo et al., 2011), methadone (Postigo et al., 2011; Rao et al., 2016; van Dyken et al., 2014; Van Dyken et al., 2016), and many others. Within prisons, these are medically prescribed to prisoners, but can be covertly diverted to other persons in custody (Schifano et al., 2018). With regard to NPS, SCRAs was and is the group most frequently reported in prisons (EMCDDA, 2018). The use of NPS and OTC and POM in prisons worsens the health and welfare of prisoners: indeed, it is associated with violence, organised crime, bullying, debt (Great Britain. Her Majesty's Chief Inspector of Prisons for England and Wales. et al., 2016; Great Britain. HM Inspectorate of Prisons for England and Wales. et al., 2017), self-harm and suicide (Prison and Probations Ombudsman, 2015). Boredom, affordability, undetectability by most traditional drug testing and wide availability compared to traditional illegal drugs may be the reasons behind the misuse of NPS and OTC and POM (Schifano et al., 2018). Reports of NPS use in prison together with misuse of OTC and POM has increased massively in recent years (Bi-Mohammed et al., 2017; Deeb et al., 2020; Vaccaro et al., 2022), with opiates, and gabapentinoids being the most frequently detected classes of drugs. Detainees reported that the use of some prescription substances provided the same highs as other illicit substances (Tompkins et al., 2009). Additionally, OTC and POM are more likely to be perceived as safe to be used; unrelated to a misusing potential (Chiappini and Schifano, 2020; Inciardi et al., 2007; Schifano et al., 2021); and easier to obtain – either by smuggling or through the prison's health services - than other illicit substances (Wish et al., 2012). If detected, the possession of non-prescribed pharmaceutical drugs was also thought by prisoners to be easier to explain (Wish et al., 2012) and less likely to attract severe punishment (Tompkins et al., 2009). Beyond variations among individual states and diverse legislative and penitentiary systems, scientific literature consistently underscores the heightened vulnerability of mental health within the prison environment (Fazel and Baillargeon, 2011). Furthermore, psychiatric disorders exhibit a higher prevalence among individuals in custody compared to the general population (Bulten et al., 2008; Fazel et al., 2017).

In this context, the utilization of NPS and the misuse of OTC and POM pose a substantial threat to the psychophysical well-being of individuals in custody. Therefore, investigating new trends in drug misuse in custodial settings over the past 20 years can shed light on the mental health conditions of those in custody and contribute to a more profound understanding of an increasingly alarming phenomenon.

2. Materials and methods

Systematic electronic searches were performed on 2 November 2022 on the following literature databases: PubMed, Scopus, and Web of Science (WoS); other relevant papers not resulting from the described searches were added from references of included articles. In the search strategy, keywords were based mainly on classes of drugs; however, keywords also included some specific drugs name such as e.g. "bupropion", "venlafaxine", "loperamide" to enhance the search effectiveness. For PubMed and WoS the following search strategy was used: ("Prison" OR "custodial setting") AND ("nps" OR "new psychoactive substances" OR "pharming" OR "bupropion" OR "quetiapine" OR "olanzapine" OR "venlafaxine" OR "loperamide" OR "biperiden" OR "dextromethorphan" OR "codeine" OR "gabapentin" OR "scopolamine" OR "hyoscine" OR "pregabalin" OR "promethazine" OR "diphenhydramine" OR "ephedrine" OR "synthetic cannabinoids" OR "synthetic opioids" OR "Fentanyl" OR "synthetic cathinones" OR "phenethylamine") NOT review NOT animal. While for Scopus a slightly different search strategy was used: (TITLE-ABS-KEY (prison) OR TITLE-ABS-KEY (custodial AND setting) AND TITLE-ABS-KEY (nps) OR TI-TLE-ABS-KEY (new AND psychoactive AND substances) OR TITLE-ABS-KEY (pharming) OR TITLE-ABS-KEY (bupropion) OR TITLE-ABS-KEY (quetiapine) OR TI-TLE-ABS-KEY (olanzapine) OR TITLE-ABS-KEY (venlafaxine) OR TITLE-ABS-KEY (loperamide) OR TITLE-ABS-KEY (biperiden) OR TITLE-ABS-KEY (dextromethorphan) OR TITLE-ABS-KEY (codeine) OR TITLE-ABS-KEY (gabapentin) OR TITLE-ABS-KEY (scopolamine) OR TITLE-ABS-KEY (hyoscine) OR TITLE-ABS-KEY (pregabalin) OR TI-TLE-ABS-KEY (promethazine) OR TITLE-ABS-KEY (diphenhydramine) OR TI-TLE-ABS-KEY (ephedrine) OR TITLE-ABS-KEY (synthetic AND cannabinoids) OR TI-TLE-ABS-KEY (synthetic AND opioids) OR TITLE-ABS-KEY (fentanyl) OR TI-TLE-ABS-KEY (synthetic AND cathinones) OR TITLE-ABS-KEY (phenethylamine) AND NOT TITLE-ABS-KEY (review) AND NOT TITLE-ABS-KEY (animal)). The systematic review was structured in accordance with the PRISMA (Shamseer et al., 2015; Page et al., 2021) guidelines. Identified studies were assessed by title/abstract and full text screening against eligibility criteria.

The eligibility criteria included the selection of exclusively original articles written in English that provide data on the population of incarcerated individuals who have misused NPS, OCT and/or POM. The selection and eligibility phase of the articles were carried out independently by G.G., S.G., R.C., and C.C., then subjected to a last cross-check by Mi. A. and M.A. All discordant cases were evaluated by C.S., P.M., and M.G. Any unsolved doubts by the team on any of the topics covered in the article were clarified directly from the author, if contactable. The data were collected in a Word table containing the first author's name and year of publication of the study, study design, demographic

variables (gender, age, psychiatric history) and details of the drugs taken (dosage and route of administration). The exclusion criteria for both selection phases were: 1) non-original research (e.g., review, metanalysis, commentary, editorial, letter to the editor without data available, and book chapter); 2) non-full-text articles (e.g., meeting abstract); 3) language other than English; 4) animal/in vitro studies; 5) articles not related to custodial setting; 6) articles not related to selected substances.

3. Results

From a total of 538 articles (PubMed = 242; Scopus = 176; WoS = 115; other sources = 5), after deduplication (n = 136), 402 records were screened. Among the articles screened, 203 were considered not relevant to the subject after reading the title and abstract, 17 were not written in English, 37 were non-original articles and 2 were case-reports. These were excluded from the analysis and placed in the appendix due their low form of evidence (Carelli et al., 2021; Strano-Rossi et al., 2021) (Appendix A). Of the 143 full-text articles assessed for eligibility, 104 did not match the inclusion criteria for our review; finally, 37 articles were included in the systematic review (Fig. 1). Studies recorded were: thirty observational studies (N=29) (Antonides et al., 2021; Bonds and Hudson, 2015; Boulger et al., 2022; Bucerius and Haggerty, 2019; Caterino et al., 2019; Cicekci et al., 2017; Deeb et al., 2020; Ford and Berg, 2017, 2018; Frinculescu et al., 2022; Giorgetti et al., 2022; Hvozdovich et al., 2020; Jalali et al., 2014; Mason et al., 2022; McKendy et al., 2021; Norman et al., 2020; Norman, Halter, et al., 2021; Norman, McKirdy, et al., 2021; Paterson and Cordero, 2006; Paul et al., 2021; Postigo et al., 2011; Rao et al., 2016; Roberts et al., 2021; Rodrigues et al., 2022; Seywright et al., 2022; van Dyken et al., 2014; Van Dyken et al., 2016; Yoganathan et al., 2022), and eight case series (N = 8) (Corazza et al., 2020; Kleis et al., 2020; Krotulski et al., 2021; Meyyappan et al., 2017; Reccoppa et al., 2004; Reeves and Ladner, 2013; Rook et al., 2016; Wikström et al., 2004).

A detailed summary of the 37 articles, organised by classes and chronological order, is included in Table 1a for NPS and Table 1b for POM/OTC. The clinical observations centred on the occurrence of

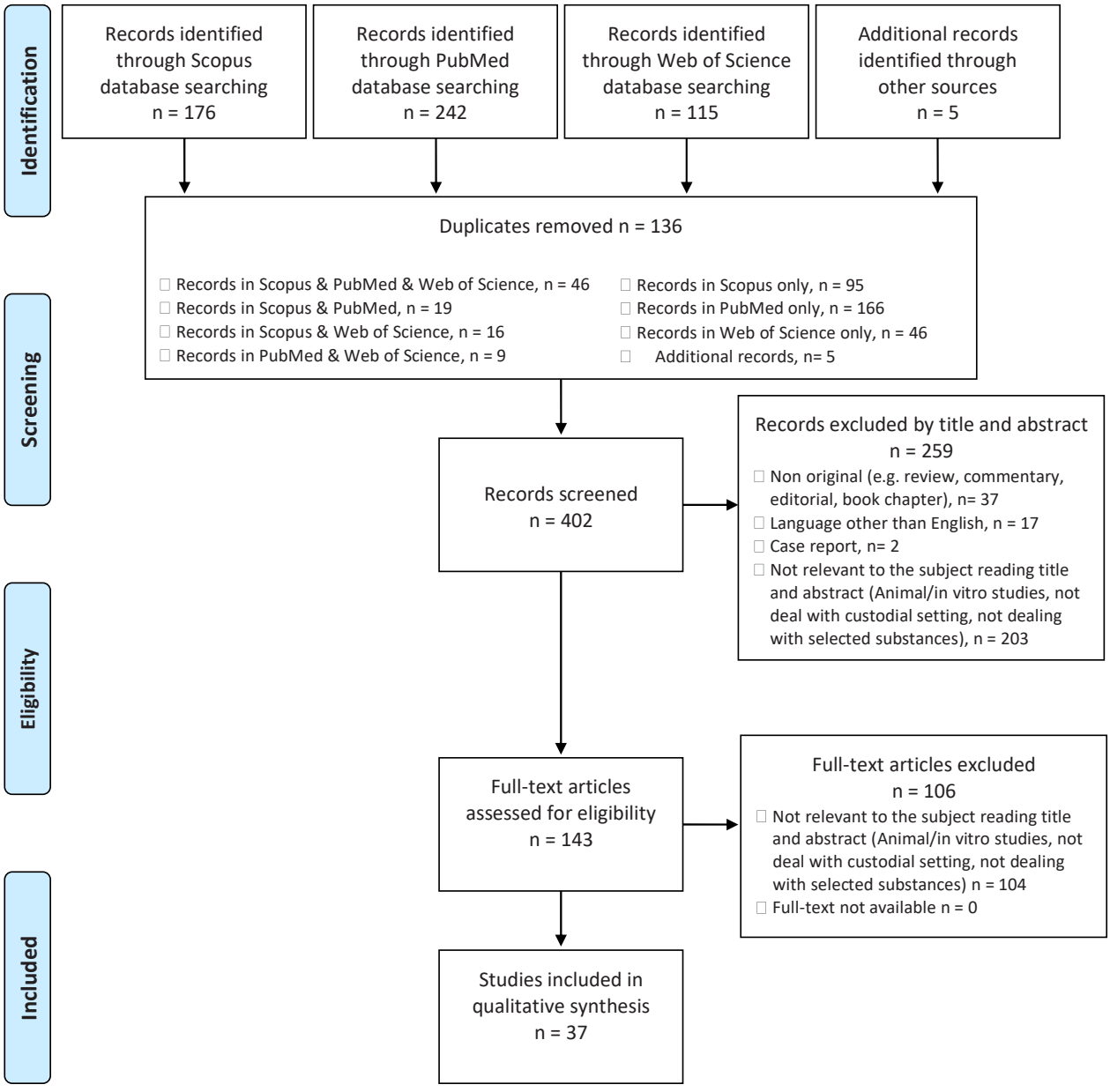

Fig. 1. Prisma flow diagram of the methodology of the systematic literature review.

Table 1a
Summary Table of included NPS articles.

NPS	Authors	Type of study	Country
			SCRAs
5 F-ADB and ADB-BUTINACA	Frinculescu et al., (2022)	Observational study	UK
MDMB-4en-PINACA and 5 F-ADB	Giorgetti et al., (2022)	Observational study	Germany
NA	Mason et al., (2022)	Observational study	UK
MDMB-4en-PINACA and 5 F-MDMB-PICA	Rodrigues et al., (2022)	Observational study	Brazil
5 F-MDMB-PINACA, MDMB-CHMICA, MMB-FUBINACA and AB-FUBINACA	Seywright et al., (2022)	Observational study	UK (Scotland)
NA	Yoganathan et al., (2022)	Observational study	UK (England)
(S)-MDMB-4en-PINACA, (S)-4 F-MDMB-BINACA, and (S)-5 F-MDMB-PICA	Antonides et al., (2021)	Observational study	UK (Scotland)
UK: MDMB-4en-PINACA and 4 F-MDMB-BINACA;Germany: metabolites of the tert-leucinate/valinate-indole/indazole- 3-carboxamides; USA: 5-F-MDMB-PICA and 4 F-MDMB-BINACA	**Norman et al., 2021a**	Observational Study	UK (Scotland and Wales); Germany and USA
5 F-MPP-PICA, 5 F-EMB-PICA, and 4 F-MDMB-BICA	**Norman et al., 2021b**	Observational study	UK (Scotland)
AB-FUBINACA, UR144, MDMB 4en Pinaca and MDMB CHMCA	Paul et al., (2021)	Observational study	UK
5 F-ADB and AB-FUBINACA metabolites	Roberts et al., (2021)	Observational study	UK
Pent-4en aNAbut-3en analogues including MDMB-4en-PINACA	Krotulski et al., (2021)	Case series	USA
NA	Corazza et al., (2020)	Case series	UK (South Wales)
5 F-ADB, FUB-AMB, FUB-AMB, MDMB-FUBINACA and AB-CHMINACA	Hvozdovich et al., (2020)	Observational study	Florida
5 F-MDMB-PINACA, 5 F-MDMB-PICA, 4 F-MDMB-BINACA and MDMB-4en-PINACA	Norman et al., (2020)	Observational study	UK (Scotland)
5 F-MDMB-PICA	Kleis et al., (2020)	Case series	Germany
4 F-MDMB-BUTINACA, 5 F-ADB, 5 F-MDMB-PICA and 4 F-MDMB-BUTINACA	Caterino et al., (2019)	Observational study	USA
5 F-AKB-48, AB-FUBINACA and MDMB-CHMICA	Ford and Berg, (2018)	Observational study	UK
5 F-MDMB-PINACA, AB-CHMINACA, APINACA, Cumyl-PEGaClone, FUB-AMB, MMB-2201and PB-22	Metternich et al., (2018)	Observational study	Germany
The third-generation synthetic cannabinoid 5 F-AKB-48	Ford and Berg, (2017)	Observational study	UK
MDMB-CHMICA	Meyyappan et al., 2017	Case series	UK
Azaindole-adamantyl-derived SCRAs	Rook et al., (2016)	Case series	UK
5 F AKB-48, MDMB-CHMICA	Bonds and Hudson, (2015)	Observational study	UK

Table 1a (*continued*)

NPS	Authors	Type of study	Country
			PIPERAZINES
N-benzylpiperazine	Wikström et al., (2004)	Case series	Sweden

Table 1b
Summary Table of included POM/OTC articles.

OTC and POM	Authors	Type of study	Country
			OPIOIDS
Fentanyl	Boulger et al., (2022)	Observational study	USA
Fentanyl	McKendy et al., (2021)	Observational study	Canada
Fentanyl	**Bucerius et al., 2019**	Observational study	Canada
NA	Rao et al., (2016)	Observational study	India
Methadone, buprenorphine, and codeine	Van Dyken et al., (2016)	Observational study	Australia
Methadone, and codeine	van Dyken et al., (2014)	Observational study	Australia
Methadone	Postigo et al., (2011)	Observational study	Spain
Morphine, codeine, and other opiate alkaloid	Paterson and Cordero, (2006)	Observational Study	UK
			GABAPENTINOIDS
Gabapentin and pregabalin	Deeb et al., (2020)	Observational study	UK (Scotland)
Gabapentin	Cicekci et al., (2017)	Observational study	Turkey
Gabapentin	Reccoppa et al., (2004)	Case series	USA (Florida)
			ANTIDEPRESSANTS
Bupropion	**Reeves et al., 2013**	Case series	USA
			OTHERS
Hyoscine N-butylbromide	Jalali et al., (2014)	Observational study	Iran

psychiatric/neurological symptoms, along with the main socio-demographic characteristics of the confined population, are reported in Table 2, with their respective prevalence rates presented in Table 3. Organic symptoms are detailed in Table 4 and, the respective prevalence rates are given in Table 5.

Most articles were related to SCRAs (N = 23). Only one article was related to the NPS piperazines class (Table 1a). OTC and POM use was detected in 13 studies, of which eight were related to prescription and OTC opioids such as methadone, fentanyl, codeine, morphine and buprenorphine. A smaller proportion was related to other prescription drugs (N = 4), such as: gabapentinoids (N = 3) and the antidepressant bupropion (N = 1). OTC were found only in one article mentioning the anticholinergic drug hyoscine N- butylbromide aka scopolamine N-butylbromide (N = 1) (Table 1b).

Demographic findings showed a predominance of males. There were only four studies reporting a mixed population, and none in women alone. The age of the subjects ranged from 21 to 49 years. A psychiatric history was recorded in five articles, mainly relating to personality disorders, anxiety disorders, neurocognitive/neurodevelopmental issues, and both psychotic and mood disorders. A history of polysubstance use was reported in most cases, including alcohol, cannabis, cocaine, amphetamines, ketamine and heroin (Table 2).

Among the most commonly reported psychiatric/neurological symptoms, it is noteworthy that violent/aggressive behaviour was observed in four articles. Alterations in the level of consciousness also was reported in four other articles. Seizures were documented in three articles as well as slurred speech reported in three other articles.

Table 2
Summary of results related to psychiatric/neurological symptoms.

Substances	Authors	Population	Mean Age (years)	Gender (M/F)	PsychiatricAnamnesis	Psychiatric/neurological symptoms
SCRAs						
5 F-ADB and ADB-BUTINACA	Frinculescu et al., (2022)	N = 17 e-cigarettes liquid	NA	NA	NA	NA
MDMB-4en-PINACA and 5 F-ADB	Giorgetti et al., (2022)	N = 1 infused paper	NA	NA	NA	NA
NA	Mason et al., (2022)	N = 158prisoners	34.82	M	Impulsivity	NPS users participated in more violent acts against prison staff members than non-users
MDMB-4en-PINACA and 5 F-MDMB-PICA	Rodrigues et al., (2022)	N = 56 infused papers	NA	NA	NA	ND
5 F-MDMB-PINACA, MDMB-CHMICA, MMB-FUBINACA and AB-FUBINACA	Seywright et al., (2022)	N = 11urine and blood	38	M	NA	Suicide (N = 3); stab wounds death (N = 1); basilar artery dissection (N = 1)
NA	Yoganathan et al., (2022)	N = 8	NA	NA	NA	NA
(S)-MDMB-4en-PINACA, (S)-4 F-MDMB-BINACA, and (S)-5 F-MDMB-PICA	Antonides et al., (2021)	N = 177 infused papers	NA	NA	NA	NA
UK: MDMB-4en-PINACA and 4 F-MDMB-BINACA; metabolites of the tert-leucinate/valinate-indole/indazole- 3-carboxamides; USA:5-F-MDMB-PICA and 4 F-MDMB-BINACA	**Norman et al., 2021a**	N = 4427 1638 infused papers and othersN = 486 (Scotland); N = 1152 (Wales)2789 urine samples: N = 570 (USA); N = 2219 Germany	NA	NA	NA	NA
5 F-MPP-PICA, 5 F-EMB-PICA, and 4 F-MDMB-BICA	**Norman et al., 2021b**	N = 126 infused papers	NA	NA	NA	NA
AB-FUBINACA, UR144, MDMB 4en Pinaca and MDMB CHMCA	Paul et al., (2021)	Air samples	NA	NA	NA	NA
5 F-ADB and AB-FUBINACA metabolites	Roberts et al., (2021)	N = 2	35	M	NA	Sudden cardiac death associated with SCRAs in vaping products (N = 2)
Pent-4en and but-3en analogues including MDMB-4en-PINACA	Krotulski et al., (2021)	N = 25 urine and blood	36.1	F = 11, M = 8, NA = 6	NA	NA
NA	Corazza et al., (2020)	N = 5	37.4	NA	NA	Complex multimodal illusions (mainly visual); auditory hallucinations
5 F-ADB, FUB-AMB, FUB-AMB, MDMB-FUBINACA and AB-CHMINACA	Hvozdovich et al., (2020)	N = 54urine and blood	45.2	M	NA	NA
5 F-MDMB-PINACA, 5 F-MDMB-PICA, 4 F-MDMB-BINACA and MDMB-4en-PINACA	Norman et al., (2020)	N = 392 Infused papers	NA	NA	NA	NA
5 F-MDMB-PICA	Kleis et al., (2020)	N = 12 urine and blood	32.33	F = 1, M = 11	ND	Changing moods; aggression confusion; erratic behaviour; mental leaps; disorientation; slowed reaction; logorrhoea and slurred speech
4 F-MDMB-BUTINACA, 5 F-ADB, 5 F-MDMB-PICA, 4 F-MDMB-BUTINACA	Caterino et al., (2019)	N= 5 infused papers	NA	NA	NA	NA
5 F-AKB-48, AB-FUBINACA and MDMB-CHMICA	Ford and Berg, (2018)	N= 5 infused papers	NA	NA	NA	SCRAs catatonic states; dystonia; aggression Ethylphenidate: anxiety; paranoia; visual disturbance; bizarre and violent behaviour; loss of fine motor control.MPA: anxiety; panic attacks. MXP: catatonic states; dystonia; aggression
5 F-MDMB-PINACA, AB-CHMINACA, APINACA, Cumyl-PEGaClone, FUB-AMB, MMB-2201 and PB-22	Metternich et al., (2018)	N = 36 infused papers and herbal material	NA	NA	NA	NA
The third-generation synthetic cannabinoid 5 F-AKB-48	Ford and Berg, (2017)	N= 98 herbal material	NA	NA	NA	NA

(*continued on next page*)

Table 2 (*continued*)

Substances	Authors	Population	Mean Age (years)	Gender (M/F)	PsychiatricAnamnesis	Psychiatric/neurological symptoms
MDMB-CHMICA	Meyyappan et al., 2017	N = 3blood	29	M	NA	Subject 2= seizure, GCS was 3/15.Subject 3= seizure, GCS was 3/15, agitation
Azaindole-adamantyl-derived SCRAs	Rook et al., (2016)	N = 4urine	NA	NA	NA	Reduced level of consciousness (N = 3); tonic-clonic seizure (N = 1); sinus tachycardia (N = 3)
5 F AKB-48 and MDMB-CHMICA	Bonds and Hudson, (2015)	N = 12,000 urine	NA	NA	NA	NA
PIPERAZINES						
N-benzylpiperazines	Wikström et al., (2004)	N = 11 urine	NA	NA	NA	NA
						OPIOIDS
Fentanyl	Boulger et al., (2022)	N = 46,308 probation clients	33.7	M= 80,5%	NA	NA
Fentanyl	McKendy et al., (2021)	N = 530 (positive N = 29)	35,72	M = 93%	Mood disorder (n = 207), psychotic disorder (n = 56), anxiety disorder (n = 170), personality disorder (n = 140), neurocognitive/ neurodevelopmental symptoms (N = 165)	NA
Fentanyl	**Bucerius et al., 2019**	N = 587	NA	M = 495; F = 92	NA	NA
Opioids	Rao et al., (2016)	N = 30Interviewed individuals	33,6	M	NA	NA
Methadone, buprenorphine, and codeine	Van Dyken et al., (2016)	Wastewater analysis (N = 437 average daily population including 45 visitors and 2 staff)	NA	NA	NA	NA
Methadone and codeine	van Dyken et al., (2014)	Wastewater analysis(N = 494 average total daily population including 29 visitors and 90 staff)	NA	NA	NA	NA
Methadone	Postigo et al., (2011)	Wastewater analysis (N =3500 people)	NA	NA	NA	NA
Morphine, codeine and other opiate alkaloids	Paterson and Cordero, (2006)	N = 227	NA	NA	NA	NA
GABAPENTINOIDS						
Gabapentin andpregabalin	Deeb et al., (2020)	N= 904 urine	NA	NA	NA	NA
Gabapentin	Cicekci et al., (2017)	N = 39:group 1 (off-label dosages of gabapentin) N = 23; group 2 (gabapentin dose in labelled indications) N = 16	Group 1: N = 23; Group 2: N = 16	M	NA	NA
Gabapentin	Reccoppa et al., (2004)	N = 5	29–45	M	Anxiety disorder (N = 1), bipolar disorder (N = 2), impulse control disorder (N = 1), antisocial personality disorder (N = 2)	Altered mental state or 'high'(N=4)
						ANTIDEPRESSANTS

(*continued on next page*)

Table 2 (*continued*)

Substances	Authors	Population	Mean Age (years)	Gender (M/F)	PsychiatricAnamnesis	Psychiatric/neurological symptoms
Bupropion	Reeves et al., 2013	N = 4	49 (N = 1), others ND	M	Depression and malingering (N = 1)	Auditory hallucinations, as multiple voices making various comments (N = 1); seizure (N = 1)
Hyoscine N-butylbromide	Jalali et al., (2014)	N = 36	33.3	M	NA	***OTHERS*** Neurological adverse effects: insomnia 30%; irritability 34%; inability to concentrate 33%; incoherent speech 32%; slurred speech 32%; amnesia 32%; agitation 31%; illogical thinking 30%; cessation of sweating 30%; apprehension 28%; visual hallucination 26%; tactile hallucination 26%; auditory hallucination 22%

Table 3
Prevalence of the main psychiatric/neurological symptoms.

Psychiatric/ neurological symptoms	Prevalence(N of articles where the symptom was reported)	Authors
Violent/aggressive behaviour	4	Ford and Berg, (2018); Mason et al., (2022); Kleis et al., (2020); Jalali et al., (2014)
Alterations in the level of consciousness	4	Ford and Berg, (2018); Kleis et al., (2020); Rook et al., (2016); Reccoppa et al., (2004)
Seizures	3	Meyyappan et al., 2017; Rook et al., (2016); Reeves et al., 2013
Slurred speech	3	Kleis et al., (2020); Jalali et al., (2014)
Hallucinations	2	Reeves et al., 2013; Jalali et al., (2014)
Anxiety	2	Ford and Berg, (2018); Jalali et al., (2014)
Suicide/suicide attempt	2	Seywright et al., (2022)

Hallucinations were noted in two articles, and the appearance of anxious symptoms in two additional articles (Table 2). It is important to emphasize that the majority of studies (N=28) did not report the psychiatric/neurological symptomatology associated with the use of NPS and POM/OTC. Therefore, the lack of information reported in these articles did not allow for the extraction of quantitative data nor the calculation of related prevalence (Table 3).

Regarding the organic symptoms (Tables 4 and 5), the most common were cardiovascular events, e.g., sinus tachycardia, bradycardia, palpitation and flushing (N = 8) etc; followed by gastrointestinal symptoms (N = 2). A total of eight death were recorded, of which seven were related to the use of the specific NPS on their own or together with traditional drugs of misuse. While there was only one POM-related death, it involved fentanyl, either used alone or with other substances e.g., heroin.

4. Discussion

4.1. NPS, OTC and POM use reported within the custodial settings

The NPS substance groups, reported in order of prevalence, were SCRAs and piperazines with the majority of articles (N = 23) focusing on the NPS class SCRAs, consistently with European and international sources (EMCDDA, 2022; UNODC, 2021). SCRAs mainly bind to the CB1 cannabinoid receptor, with a greater affinity and potency when compared to delta-9-tetrahydrocannabinol (THC). These receptors are predominantly responsible for the misuse-related psychoactive effects of these drugs; however, little is known about the detailed pharmacology/toxicology. The first evidence of the use of SCRAs in prison is traceable to 2015 in England (Bonds and Hudson, 2015). Since then, there has been a steady increase in the number of the publications on the topic, with a peak between 2021 and 2022 (Table 1a), likely to correspond to an uptrend in the use of SCRAs in prison. The use of such substances seems to be more prevalent in the custodial setting than in the general population. However, if we look at vulnerable populations such as homeless and teenagers under 16 years sold, we continue and start to see a high level of SCRAs consumption, respectively (Frinculescu et al., 2022). Use of the latter helps prisoners coping with their condition, relieving boredom, and mitigating stress and anxiety. SCRAs remain the NPS class with the highest number of compounds, more than 200 (Pasin et al., 2022), which are dynamically evolving, with only a limited number staying in the illicit market for extended periods e.g., 5 F-MDMB-PINACA (aka 5 F-ADB). Changes in their molecular structure are aimed at circumventing international and country specific/national NPS legislation. For instance, shifting patterns of availability and consumption in Europe are often detected after specific SCRAs are placed under national control in China, where these substances are mainly produced. 5 F-ADB, AB-FUBINACA ADB-FUBINACA, and AMB-FUBINACA predominated the market in the UK, Germany, and USA until late 2018. Since that date, other SCRAs not yet under legislative control in China became more popular. 5 F-MDMB-PICA re-emerged, in both German prison and local markets, after being detected for the first time in 2016. Likewise, 4 F-MDMB-BINACA made its appearance (Norman et al., 2020; Norman et al., 2021a, 2021b). Once 5 F-MDMB-PICA and 4 F-MDMB-BINACA, in 2019, were put under review for international control, a spike in the prevalence of MDMB-4en-PINACA was seen in the UK, Germany, and USA. MDMB-4en-PINACA was the most detected SCRA in Scottish prisons and in Germany in 2020 (Norman et al., 2021a, 2021b). It is explicit that changes in the availability in the global and local market are closely reflected in prisons. Moreover, changes in their chemical structure pose challenges in their forensic detection, making it difficult to provide scientific evidence to support identification using drug-screening techniques in prison. Furthermore, reference materials are rarely readily available and only little is known about the pharmacology/toxicology of many of them. In addition to that there are also challenges related to unconventional dosage forms for the dissemination, concealment, and

Table 4
Summary of results related to organic symptoms.

Substances	Authors	Population	Mean Age (years)	Gender (M/F)	Toxicologic Anamnesis	Other drugs /substances detected	Organic symptoms
SCRAs							
5 F-ADB and ADB-BUTINACA	Frinculescu et al., (2022)	N = 17 e-cigarettes liquid	NA	NA	NA	Nicotine (N = 87); THC (N = 1); CBD (N = 1); and THC and CBD (N = 6)	NA
MDMB-4en-PINACA and 5 F-ADB	Giorgetti et al., (2022)	N = 1 infused paper	NA	NA	NA	AP-237 (synthetic opioid)	NA
NA	Mason et al., (2022)	N = 158prisoners	34.82	M	23% NPS; 11% traditional substance; 23% both; 43% no substance use	NA	NA
MDMB-4en-PINACA and 5 F-MDMB-PICA	Rodrigues et al., (2022)	N = 56 infused papers	NA	NA	NA	NA	NA
5 F-MDMB-PINACA, MDMB-CHMICA, MMB-FUBINACA and AB-FUBINACA	Seywright et al., (2022)	N = 11urine and blood	38	M	NA	Zopiclone, methadone, mirtazapine, alcohol, diazepam, lorazepam and amitriptyline	Death (N = 4); basilar artery dissection (N = 1)
NA	Yoganathan et al. (2022)	N = 8	NA	NA	NA	NA	Death (N = 8)
MDMB-4en-PINACA and 4 F-MDMB-BINACA; tert-leucinate- and valinate-indole- and indazole- 3-carboxa-mides; 5-F-MDMB-PICA and 4 F-MDMB-BINACA	Norman et al. 2021a	N = 4427 1638 infused papers and othersN = 486 (Scotland); N = 1152 (Wales)2789 urine samples: N = 570 (USA); N = 2219 Germany	NA	NA	NA	NA	NA
UK: MDMB-4en-PINACA and 4 F-MDMB-BINACA; metabolites of the tert-leucinate/ valinate-indole/ indazole- 3-carboxa-mides; USA:5-F-MDMB-PICA and 4 F-MDMB-BINACA	Norman et al. 2021a	N = 4427 1638 infused papers and othersN = 486 (Scotland); N = 1152 (Wales)2789 urine samples: N = 570 (USA); N = 2219 Germany	NA	NA	NA	NA	NA
5 F-MPP-PICA, 5 F-EMB-PICA, and 4 F-MDMB-BICA	Norman et al., 2021b	N = 126 infused papers	NA	NA	NA	NA	NA
AB-FUBINACA, UR144, MDMB 4en PINACA and MDMB CHMCA	Paul et al., (2021)	Air samples	NA	NA	NA	NA	Cardiac death (N = 2)
Pent-4en and but-3en analogues including MDMB-4en-PINACA	Krotulski et al., (2021)	N = 25 urine and blood	36,1	F = 11, M = 8, ND = 6	Case 5: history of lupus; heavy ethanol and SCRAs use; Case 15: Suspected drugoverdose; history of synthetic drug use; Case 17: homelessindividual; history of SCRAs use; Case 18: possible illicit drug misuse; possible SCRAs use; Case 19: DUI; suspected SCRAs use; Case 21: suspected drugoverdose; possible "Mojo" use; history of diabetes	Case 15: ethanol; methamphetamine; amphetamine; and nicotine;Case 16: THC; fentanyl; and nicotine; Case 18: ethanol; Case 25: fentanyl; xylazine; diazepam; morphine; and naloxone	MDMB-4en-PINACA causing/ contributing to impairment /death
(S)-MDMB-4en-PINACA, (S)-4 F-MDMB-BINACA, and (S)-5 F-MDMB-PICA	Antonides et al., (2021)	N = 177 infused papers	NA	NA	NA	NA	NA
5 F-ADB and AB-FUBINACA metabolites	Roberts et al., (2021)	N = 2	35	NA	NA	NA	Sudden cardiac death associated with SCRAs in vaping products (N = 2)

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Table 4 (*continued*)

Substances	Authors	Population	Mean Age (years)	Gender (M/F)	Toxicologic Anamnesis	Other drugs /substances detected	Organic symptoms
5 F-ADB, FUB-AMB, FUB-AMB, MDMB-FUBINACA and AB-CHMINACA	Hvozdovich et al., (2020)	N = 54urine and blood	45.2	M	NA	NA	Death (N=54)
5 F-MDMB-PINACA, 5 F-MDMB-PICA, 4 F-MDMB-BINACA and MDMB-4en-PINACA	Norman et al., (2020)	N = 392 Infused papers	NA	NA	NA	NA	NA
NA	Corazza et al., (2020)	N = 5	37.4	NA	NA	NA	NA
5 F-MDMB-PICA	Kleis et al., (2020)	N = 12 urine and blood	32.33	F=1, M=11	NA	Alcohol (N = 6); cannabis (N = 6), other SCRAs (N = 6)	Death (N =3); balance deficiencies and ocular effects.
4 F-MDMB-BUTINACA, 5 F-ADB, 5 F-MDMB-PICA, 4 F-MDMB-BUTINACA	Caterino et al., (2019)	N = 5 infused papers	NA	NA	NA	NA	NA
5 F-AKB-48, AB-FUBINACA and MDMB-CHMICA	Ford and Berg, (2018)	N = 5 infused papers	NA	NA	NA	Ethylphenidate; methiopropamine and methoxiphenidaine (MXP); etizolam; cocaine; methylphenidate; cutting agents: lignocaine; benzocaine and procaine	SCRAs: dystonia; respiratory depression; hypotension and tachycardiaEthylphenidate: chest pain; loss of fine motor control; a high risk of bacterial infection and local tissue damage. MPA: tachycardia; sweating; headaches; nausea; difficulty breathing and vomiting; MXP hypertension; tachy- cardia
5 F-MDMB-PINACA, AB-CHMINACA, APINACA, Cumyl-PEGaClone, FUB-AMB, MMB-2201 and PB-22	Metternich et al., (2018)	N = 36 infused papers and herbal material	NA	NA	NA	NA	NA
The third-generation synthetic cannabinoid 5 F-AKB-48	Ford and Berg, (2017)	N= 14herbal material	NA	NA	NA	Mephedrone, PB-22 and STS-135	NA
MDMB-CHMICA	Meyyappan et al., 2017	N = 3blood	29	M	Use of SCRAs	Subject 1: mirtazapine; propranolol; Subject 2: quetiapine; promethazine, cocaine; Subject 3: olanzapine	Subject 1: hypercapnia, bradycardiaSubject 2, 3: seizure
Azaindole-adamantyl-derived SCRAs	Rook et al., (2016)	N = 4urine	NA	NA	NA	Dihydromorphine; morphine; buprenorphine; methadone; amitriptyline; mirtazapine; pregabalin; olanzapine	Tonic-clonic seizure (N = 1); sinus tachycardia (N = 3).
5 F AKB-48 and MDMB-CHMICA	Bonds and Hudson, (2015)	N = 12,000 urine	NA	NA	NA	Antidepressants: amitriptyline; citalopram: fluoxetine; mirtazapine; and sertraline; Antipsychotics: olanzapine and quetiapine; Benzodiazepines: diazepam; Mood stabilizers: gabapentin and pregabalin; Opioids: buprenorphine; codeine; dihydrocodeine; heroin; methadone; and tramadol;Other substances of abuse: amphetamines; cannabis; and cocaine	NA
PIPERAZINES							
N-benzylpiperazines	Wikström et al., (2004)	N = 11urine	NA	NA	NA	Amphetamines, MDMA, MDA and THC	N-benzylpiperazine contributed to the death (N = 1)

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Table 4 (*continued*)

Substances	Authors	Population	Mean Age (years)	Gender (M/F)	Toxicologic Anamnesis	Other drugs /substances detected	Organic symptoms
							OPIOIDS
Fentanyl	Boulger et al., (2022)	N= 46,308 probation clients	33.7	M= 80,5%	20.5% urine positive to drug test on record (most commonly cannabis 69%).13.7% recorded placement in an alcohol or other drug treatment program	167 deaths:fentanyl (N = 145); heroin (N = 99), fentanyl and heroin (N = 77); multiple substances (N = 138)	Deaths (N = 167)
Fentanyl	McKendy et al., (2021)	N = 530 (positive N = 29)	35.72	M = 93%	NA	Heroin (N = 76);Methadone/ Suboxone (N = 54); Stimulants (N = 66);Non-opioid POM (N = 182); Cannabis (N = 56)	Medical response: CPR was used (N = 90); AED was used (N = 68); Naloxone was used (N = 280);
Fentanyl	Bucerius et al., 2019	N = 587	NA	M = 495; F = 92	Substance use (M: 85–90 %, F: 90–100 %)	ND	NA
Opioid	Rao et al., (2016)	N = 30Interviewed individuals	33.6	M	In treatment with buprenorphine (N = 25) and both buprenorphine and methadone (N = 76)	Cannabis (N = 22), 'Charas' (a preparation containing cannabis) (N = 1)	NA
Methadone, buprenorphine, and codeine	Van Dyken et al., (2016)	Wastewater analysis (N = 437 average daily population including 45 visitors and 2 staff)	NA	NA	NA	Daily use of methamphetamine, and sporadic detection of ketamine and methylone	NA
Methadone and codeine	van Dyken et al., (2014)	Wastewater analysis(N = 494 average total daily population including 29 visitors and 90 staff)	NA	NA	NA	Cannabis; ketamine, amphetamines/ methamphetamines	NA
Methadone	Postigo et al., (2011)	Wastewater analysis (N =3500 people)	NA	NA	NA	Alprazolam (129 doses/day/ 1000 inh); ephedrine (46 doses/day/1000 inh); cannabis (33 doses/day/ 1000 inh.) and cocaine (3 doses/day/1000 inh). Sporadic consumption of heroin; amphetamine; methamphetamine; ecstasy	NA
Morphine, codeine and other opiate alkaloids	Paterson and Cordero, (2006)	N = 227	NA	NA	NA	NA	NA
							GABAPENTINOIDS
Gabapentin and pregabalin	Deeb et al., (2020)	N= 904 urine samples	NA	NA	NA	81% of urine samples positive for illicit or non-prescribed drugs: benzodiazepines (67%); opiates (57%); and cannabis (47%); 44% of urine samples were positive for methadone. Urine samples positive for antiepileptic drugs N = 164 (gabapentin (N = 118); pregabalin (N = 32); both drugs (N = 12); levetiracetam (N = 4); lamotrigine (N = 3); valproic acid (N = 3); carbamazepine (N = 2); topiramate (N = 1); more than 1 anti-epileptic drug (N = 15)(26% of them non-prescription cases)	NA
Gabapentin	Cicekci et al., (2017)	N = 39:group 1 (off-label dosages of gabapentin) N = 23; group 2	Group 1: N = 23; Group	M	Group 1: substance addiction – DSM IV-TR (N = 10); substance abuse	NA	NA

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Table 4 (*continued*)

Substances	Authors	Population	Mean Age (years)	Gender (M/F)	Toxicologic Anamnesis	Other drugs /substances detected	Organic symptoms
		(gabapentin dose in labelled indications) N = 16	2: N = 16		DSM IV-TR (N = 13); gabapentin misuse DSM IV-TR (N = 23)		
Gabapentin	Reccoppa et al., (2004)	N = 5	29–45	M	Cocaine use or dependence prior to imprisonment (N = 5)	Antidepressants (tricyclics and selective serotonin reuptake inhibitors); valproic acid; and carbamazepine	NA
							ANTIDEPRESSANTS
Bupropion	**Reeves et al.; 2013**	N = 4	49 (N = 1); others ND	M	Stimulant use (N = 1)	Quetiapine; mirtazapine; triazolam; lorazepam; diazepam and valproic acid	NA
OTHERS							
Hyoscine N-butylbromide	Jalali et al., (2014)	N=36	27–42	M	Cigarette smokers (N = 36); substance use (N = 36); methadone maintenance therapy (N = 35)	NA	Gastrointestinal AE: dry mouth 36%; dry throat 36%; diminished bowel movement 14% Cardiovascular AE: palpitation 31%; flushing 31%Ocular AE: blurred vision 26%; photophobia 21%

Table 5
Prevalence of the main organic symptoms.

Organic symptoms	Prevalence(N of articles where the symptom was reported)	Authors
Death	8	Boulger et al., (2022); Seywright et al., (2022); Roberts et al., (2021); Yoganathan et al., 2021; Krotulski et al., (2021); Hvozdovich et al., (2020); Kleis et al., (2020); Paul et al., (2021)
Cardiovascular symptoms	7	Ford and Berg, (2018); Meyyappan et al., 2017; Rook et al., (2016); Jalali et al., (2014); Seywright et al., (2022); Wikström et al., (2004); Paul et al., (2021)
Gastrointestinal symptoms	2	Ford and Berg, (2018); Jalali et al., (2014)
Ocular symptoms	2	Kleis et al.;(2020); Jalali et al.; (2014)
Respiratory symptoms	2	Ford and Berg, (2018); Meyyappan et al., 2017

use of NPS - such as the use of infused papers (Ford and Berg, 2018) and e-cigarettes liquid (Frinculescu et al., 2022).

The use of the NPS, N-benzylpiperazine was reported in only one study (Wikström et al., 2004). N-benzylpiperazine is a stimulant drug mediating the actions of dopamine, norepinephrine and/or serotonin, mimicking the effects of traditional drugs such as cocaine, amphetamine, methamphetamine, and ecstasy (EMCDDA, 2022). This finding was particularly unusual, given that in prison, substances with a depressant effects are usually preferred to those e having stimulant effects (Vaccaro et al., 2022).

The OTC and POM misused in custodial settings, reported in order of prevalence, were opioids (N = 8), gabapentinoids (N = 3) antidepressants (N = 1), and scopolamine (N = 1) (Table 1a). Methadone, fentanyl, codeine, morphine and buprenorphine were the most misused opioids (Table 1a). This finding is in line with the observation that up to one-third of persons in custody may regularly be prescribed these substances (Kastelic et al., 2012), which can then be easily diverted. Fentanyl use and overdoses in custodial settings have been consistently increasing since 2012 (McKendy et al., 2021, Boulger et al., 2022). Fentanyl and its analogues activate the opioids receptors and can have more than 100 times potency compared to morphine. Due to the high potency, it was found that prisoners typically mix it with other substances such as baby powder or powdered sugar. The drug overall was perceived as 'scary', but on the other hand, from anecdotal reports, it seemed to be 'everywhere' It also emerged that some fentanyl use was unintentional, due to traditional drugs of misuse such as heroin and cocaine being laced with it (Bucerius and Haggerty, 2019). In two studies the daily quantity of methadone and/or buprenorphine administered to prisoners undergoing maintenance therapy was compared with the amount estimated to be consumed using waste waters analysis (WWA) data (Van Dyken et al., 2014, 2016). In the study from 2014 only the level of methadone was targeted, and it was found that the quantity consumed deviated by no more than roughly two doses compared to the usual presctibed one (van Dyken et al., 2014). The more recent study also targeted buprenorphine, likely related to awareness of its misuse in the community. The level of buprenorphine misuse was found to be higher than that of methadone (van Dykenet al., 2014). The rationale behind that is to be found in the difference of the dispensed pharmaceutical forms. For instance, methadone is given principally in liquid form but buprenorphine as a sublingual film or tablet, which make them easier to divert or introduce illicitly in prison. Additionally, use of codeine emerged from WWA of these two studies (Van Dyken et al., 2014, 2016), due to the lack of its prescribing schedule it was unclear whether the use was licit or illicit. However, due to the high concentration found and the known concern of its misuse in general population it was likely to be misused in this context too. The use of alternative analgesic opioids with a reduced misue potential and diversion rate such as tapentadol or buprenorphine/naloxone should be considered in such populations. This aspect is analysed in further depth in Section 4.4.

Although the most reported POM being misused worldwide are stimulants e.g., methylphenidate, and central nervous system depressants e.g., benzodiazepines, the misuse of pregabalin and its structurally-related compound gabapentin have also risen significantly in the general population as well as in custodial settings.

Gabapentinoids are being perceived as possessing a favourable safety profile, within a context of high availability levels due to increased levels of prescribing (Chiappini and Schifano, 2020; Evoy et al., 2021). This trend has been documented among opioid misusers and since 2004 also in custodial setting (Reccoppa et al., 2004). Pregabalin and gabapentin are being ingested at higher than recommended dosages to achieve psychotropic effects, including euphoria and feelings of relaxations and calmness (Chiappini and Schifano, 2016; Evoy et al., 2021;

Schifano, 2014; Schifano et al., 2018). It is likely that in this specific setting these substances are misused to achieve the latter effect, for the same reasons mentioned for the SCRAs. An additional reason behind their appearance in prisons could be related to the fact that people suffering from opioid addiction might be more prone their misuse, to either to reinforce their effect or reduce withdrawal symptoms, such as pain, anxiety, or insomnia (Hoffman and Besson, 2021).

Bupropion diversion and misuse were identified. The mechanism of reinforcement of misuse of bupropion is related to the inhibition of the reuptake of dopamine and norepinephrine neurotransmitters. If this is consumed orally reinforcing propriety should not arise; however, its potential for misuse is demonstrated by different routes of administration being used. Indeed nasal insufflation is the preferred route, used both in the general population and in custodial settings, as it is associated with a rapid and strong effect (Chiappini and Schifano, 2020; Hilliard et al., 2013; Schifano and Chiappini, 2018; Stall et al., 2014) since it bypasses first pass metabolism, resulting in a higher plasma concentration.

Interestingly the only OTC recorded was the anticholinergic drug scopolamine N-butylbromide, commonly used orally for its antispasmodic effect (Jalali et al., 2014). Scopolamine, similarly to other anticholinergic drugs, e.g., benztropine, might be misused for its psychotropic effects, e.g., to achieve a 'high' or euphoria, to elevate energy and mood and to increase social interaction. However, it is more likely that the N-butylbromide, derivative of scopolamine is smoked in order to allow the free base to pass the blood.brain barrier and, therefore, to achieve hallucinogenic-like effects (Frascht et al., 2007).

It is important to note that the changes in substance use may happen quickly; therefore, trends may already have been changed since November 2022, when the literature searches were conducted.

4.2. Psychiatric symptoms and implications related to the use of NPS, OTC, and POM

The majority of items covered by this review indicate that in custodial settings, the most encountered psychiatric/neurological symptoms related to SCRA consumption include violent/aggressive behaviour and alterations in consciousness. Although a high rate of violent behaviour has also been observed in the general population (Fazel et al., 2018; Shafi et al., 2017), the clinical presentation related to SCRA intake, comprises euphoria, feelings of well-being, calmness, relaxation, increased creativity, and hallucinatory experiences (Papanti et al., 2013; Spaderna et al., 2013). Conversely, SCRAs-related acute intoxication is characterized by agitation/anxiety and auditory hallucinations (Schifano et al., 2015, 2017; Hermanns-Clausen et al., 2013; Winstock and Barratt, 2013). This paradox is intriguing, as it appears that violent/aggressive behaviour associated with SCRAs consumption is particularly pronounced in the prison population. Considering the characteristics of such populations, where high rates of antisocial personality disorder and psychotic disorders are more common (Fazel, 2002), the use of these substances may exacerbate aggressive behaviours (Schifano et al., 2017; Schifano et al., 2021). Furthermore, it is important to consider how the challenging conditions of incarceration, which can already be considered a stressful factor (Semenza et al., 2019), might, under the influence of substances, contribute to aggressive outbursts.

The most reported psychiatric/neurological symptoms related to the use of piperazines in in the general population, according to the available literature, include temperamental alterations with dysphoria, increase in vigor/activity, confusion, anxiety, depression, paranoia, and auditory hallucinations (Arbo et al., 2012). There is a lack of data on specific symptoms related to their use in custodial settings, therefore a comparison is not possible.

Regarding psychiatric/neurological symptoms related to the misuse of opioids such as codeine, methadone, morphine, buprenorphine), none of the included articles did not have reported any data related to such symptoms. Therefore, it is not possible to make a comparison with data from the general population. Certainly, the same prescribing recommendations as those for the general population apply to the detainee population, which is to carefully assess the benefits and risks in opioid prescribing and limit its prescription only to cases of extreme necessity, avoiding individuals with past or current substance misuse or untreated psychiatric disorders (Carinci, 2020; Dart et al., 2021).

There is a lack of available data on the effects of misused gabapentinoids in the prison population. Only one study (Reccoppa et al., 2004) reported altered mental state or 'high'. In this case as well, it is not possible to draw a comparison with the general population, where gabapentin and pregabalin are known to be used for seeking either relaxation or euphoria (Hägg et al., 2020).

The findings presented here have revealed that bupropion misuse in custodial setting induced auditory hallucinations, as multiple voices making various comments and anger outburst (Reeves et al., 2013). It is known that in the general and prison populations, bupropion is misused for its "cocaine-like feel and taste", through intranasal administration (Hilliard et al., 2013; Reeves et al., 2013). However excessive intranasal misuse of bupropion could then produce alterations of feelings and mood and induce psychotic symptoms. Users describe administration of doses between one and six times the maximum recommended daily dose (Naglich et al., 2019) with instances of up to 4500 mg/day intravenously (Strike & Hatcher 2015) or 1200 mg/day intranasally (Reeves et al., 2013). An additional study also indicated a notable misuse of this drug within the detainee population due to its stimulant effects (Aikoye et al., 2023), although the results are insufficent to draw any definitive conclusions.

Concerning the misuse of hyoscine N-butylbromide tablets, we have highlighted issues related to speech impairment accompanied by agitation, illogical thinking, and hallucinations. This finding is consistent with those in the general population where the misuse of anticholinergics, including also benztropine, induces symptoms of motor agitation with psychosis, paranoia, and hallucinations (Chiappini et al., 2022). It is mostly smoked but the dosages at which the psychotropic effect occurs are unknown (Chiappini et al., 2022).

The symptoms highlighted by this review may be indicative of various psychiatric and medical conditions and not necessarily isolated ones. Certainly, specific NPS such as SCRAs and cathinones, as well as stimulant drugs, might be associated with aggressive behaviour, but, on the other hand, an aggressive behaviour may be a symptom of a conduct, personality or psychotic disorder (Schifano et al., 2017; Schifano et al., 2021). Furthermore, anxiety and hallucinations could be related to the use of NPS, POM and OTC, but also be worsening pre-existing symptoms during custody. Indeed, prevalence rates for common mental disorders in custodial settings according to the specific mental disorder and the specific population variably range up to 90% (Gómez-Figueroa and Camino-Proaño, 2022), highlighting the importance of early psychiatric assessment and interventions in these settings.

To date, specific guidelines or therapeutic recommendations on how to treat psychiatric/neurological symptoms induced by NPS are lacking, both in the general and among detained populations. Currently, the treatment of NPS-induced conditions relies on a case-by-case management approach for observed symptoms, with management strategies typically limited to supportive and symptomatic care due to the scarcity of published data on alternative treatment modalities (Kersten 2015). In the absence of specific guidelines for the treatment of NPS-induced conditions, referral is made to guidelines and literature regarding the management of psychomotor agitation crises (Vieta et al., 2017), delirium (Nice 2023), substance-induced respiratory depression (Nagappa et al., 2017; Brett and Murnion, 2015), and seizures (Shellhaas 2019). While these are common practices in the general population, some specific precautions are suggested for the unique custodial setting (Fazel et al., 2016; Santora et al., 2014; National Guideline Centre, 2016) where high levels of distress and disorder are associated with poor health outcomes including hypertension, infectious diseases,

stress-related diseases, and mental health problems (Wallace et al., 2020).

Overall, the emergence of NPS is undeniably reshaping clinical and psychopathological profiles compared to traditional substances of misuse (Martinotti et al., 2021; 2015b). A mounting body of evidence supports the potential for severe psychiatric and physical consequences associated with NPS consumption (Schifano et al., 2017; Simonato et al., 2013, 17), manifesting in both acute and chronic psychopathological presentations (Nelson et al., 2014; Schifano et al., 2015). This shift can primarily be attributed to the higher affinity and potency of NPS receptors compared to traditional substances (Schifano et al., 2017; Papanti et al., 2013). Consequently, the results of unpredictable clinical presentations might pose a significant risk factor for violence and aggression in individuals with major mental disorders (Fazel et al., 2018; Shafi et al., 2017). Of particular concern is the heightened risk of precipitating *de novo* psychosis in psychosis-prone or vulnerable individuals or exacerbating prodromal psychotic syndromes. Additionally, the emergence of new forms of induced chronic psychoses, such as "Spiceophrenia" (Papanti et al., 2013) and Substance-Related Exogenous Psychosis (SREP) (Martinotti et al., 2021), raises further alarm. These novel diagnostic categories encompass persistent forms of psychoses induced by substances, distinctly separate from schizophrenia (Martinotti et al., 2021).

4.3. Organic symptoms related to the use of NPS, OTC, and POM

The use of drugs in custodial settings affects the conditions of individuals in detention, with significant health risks, which can be not only psychological, but also physical, e.g., presentation of organic symptoms, or the spread of infectious viral diseases due to sharing of syringes. In contrast to the neurological/psychiatric symptoms, organic symptoms observed in the incarcerated population closely mirror those found in the general population. For example, organic symptoms due to SCRAs intoxication reported in prison, included cardiovascular events e.g., sinus tachycardia, cardiac arrest. Simultaneously extensive literature indicates a high incidence of death and cardiac arrest associated with SCRAs use also in the general population, including severe cardiotoxic effects, dysrhythmias, ST-segment elevation, angina, and myocardial infarction (Mira et al., 2011; Schifano et al., 2016; Kersten et al., 2014).

The present study reveals that gastrointestinal disorders such as nausea and vomiting, are commonly reported in the prison population However, a notable difference is the prevalence of serious effects such as hypokalemia, toxic hepatitis/liver failure, acute kidney injury, rhabdomyolysis, hyperthermia, and serotonin syndrome, more frequently reported in the general population (Kersten et al., 2014) but absent or rare among detained individuals. This discrepancy is likely due to the limited number of case reports and studies focusing on this specific population.

Reports piperazine use in the general population include seizures, severe overdose, cases leading to respiratory acidosis, renal impairment, rhabdomyolysis, multiorgan failure (Gee et al., 2010; Kersten et al., 2014) and, in some cases, death (Elliot et al., 2016; Arbo et al., 2012). The only documented case found through our search indicates that their use might have contributed to death, however piperazines were consumed in association with amphetamines, MDMA, MDA and THC. Due to the lack of data on the incarcerated population, no specific comparisons can be drawn with the general population.

The toxic effects of NPS are more concerning and unpredictable when compared to traditional substances of misuse. This is due to their action on different systems with various mechanisms, leading to neurotoxic effects, renal insufficiency, hyperthermia, and potential progression to seizures, stroke, serotonin syndrome, as well as various cardiac events including myocardial infarction and fatal arrhythmias, posing a significant risk of mortality (Radaelli et al., 2021; German et al., 2014; Simão et al., 2022). Additionally, a markedly high rate of suicidality is associated with NPS use (Chiappini et al., 2021). Furthermore, as noted in the previous Section (4.3), the health risks for the incarcerated population in that unique environment exacerbate the toxic effects of the use of NPS, OTC and POM (Fazel et al., 2016; Wallace et al., 2020).

A common trend we must acknowledge is that the use of NPS, OTC and POM is more than often associated with the concomitant use of other NPS, OTC/POM (illicitly prescribed or not) and traditional drugs of misuse. Therefore, is extremely complex to discern between the actual causes of organic as well as psychiatric/neurologic symptoms.

4.4. Recommendations and possible future trends in substance use within the custodial settings

The surge in use of NPS and in the misuse of OTC and POM in custodial settings urgently requires greater attention from governments. New research, such as e.g. understanding the long-term effects of NPS on human health, and preventive strategies, such as e.g., figuring out how to enable better risk management to enhance early warning systems for law enforcement and policy makers, are needed. The complexity and variability of these substances makes an evidence-based approach crucial. Prevention strategies should involve not only public education, but also the implementation of stricter policies and regulations for substance control. Interventions such as implementation of new prescribing guidelines involving the administration of substances with reduced misuse potential and diversion rates should be considered. For instance, tapentadol, a centrally acting analgesic, which combines two mechanisms of action (namely μ-opioid receptor (MOR) agonism and noradrenaline reuptake inhibition), could be a better alternative to Schedule II analgesics, e.g., hydrocodone, morphine, fentanyl, oxycodone, and tramadol (Butler et al., 2015; Dart et al., 2012; Vosburg et al., 2020) for individuals in custodial settings. Furthermore, the prescription of buprenorphine/naloxone formulation should be preferred to buprenorphine alone, as the opioid antagonist naloxone could help preventing intranasal and intravenous buprenorphine misuse (Kastelic et al., 2012). It has been demonstrated that in the long term, use of such formulation leads to a reduction in negative outcomes, including accidental overdoses (Molero et al., 2018) and serious reoffending (Chang et al., 2016). Recording the prescribing schedule of OTC and POM already known to have a misuse potential such as codeine should be observed. As it emerged from one study, when records of the prescribing schedule of an OTC or POM are available is possible to back calculate the amount of illicitly sourced pharmaceuticals using WWA (Van Dyken et al., 2016) and, therefore, monitor and measure substance use in prison. More generally, if this approach were to be applied to any OTC and POM, it could be useful in unravelling new trends in the misuse of such substances in custodial settings. Administration under supervision of a healthcare professional, such as nurse or pharmacist should be considered for pharmaceuticals with misuse potential. Inclusion of POM and OTC with misuse potential, as well as the most recent NPS appeared on the market, into mandatory drug testing in prisons should be implemented. Advances in technology for detecting and preventing drugs use, such as improved screening methods and surveillance tools, should become more prominent in custodial settings.

Throughcare is a crucial component of the continuum of care for people exiting correctional facilities, especially for individuals struggling with substance use disorders (SUD) and mental health issues in prisons. Indeed, in the critical transition from incarceration to community-based services is paramount ensuring continuity of care, helping preventing relapses and mitigating the risk of overdose, self-harm, or involvement in criminal activity. Evidence from past work carried out in Europe indicated that the implementation of throughcare services for this group of patients were limited and ineffective in some EU member states (MacDonald et al., 2012). To date, there is still no universal agreement among experts regarding the delineation of these programs, the minimum standard of service provision, the optimal practices to be incorporated, or the appropriate methods for their financing, provision, oversight, and evaluation (Jamin et al., 2021;

Majeed et al., 2023). However, current research suggests that individuals in this patient category would benefit from continuity of care transitioning from incarceration to community settings; this transition should involve personalized case management tailored to address concurrent mental health disorders and SUD (Edwards et al., 2022; Vandevelde et al., 2020). Essential factors for successful treatment of patients include pre-release planning, adherence to pre-scheduled release dates, provision of medications to bridge the gap between jail release and intake at community, and the exchange of treatment-related information among agencies. While factors challenging the continuity of care are social determinants of health, there are also significant barriers to treatment continuity encompassing issues related to shelter, food security, employment, transportation (Kendall et al., 2018; Stopka et al., 2022).

An additional point is the need of a risk assessment for violence in prisons, which appears to be crucial for maintaining safety and security within correctional facilities and facilitating the rehabilitation of offenders for their eventual reintegration into society (Magaletta et al., 2016). This assessment typically involves evaluating various factors that may contribute to violent incidents among inmates, staff, or both. Firstly, they should include individual risk factors associated with inmates, including prior history of violence, gang affiliation, substance misuse, mental health issues, disciplinary record, and demographic characteristics. Secondly, environmental factors regarding the physical environment of the prison, such as overcrowding, inadequate staff-to-inmate ratios, poorly maintained facilities, access to weapons or contraband, and the layout of the prison can all contribute to heightened levels of violence. A third group of factors include staffing and quality of training provided to correctional officers, e.g., conflict resolution techniques, de-escalation strategies, and proper use of force protocols to prevent and respond to violent incidents. Finally, programming intervention strategies aiming at reducing violence is important. This includes programs focused on anger management, substance misuse treatment, mental health counselling, vocational training, and education (European Union, 2021).

Finally, increasing access to treatment for individuals using NPS or misusing OTC and POM involves a multi-faceted approach that addresses various aspects of the issue. Strategies should include: I) Education and Awareness, such as awareness campaigns aiming to educate prisoners about the risks and consequences of NPS use and OTC and POM misuses; programs offering counselling and peer support networks. II) Specialized treatment services, developing programs tailored to the unique challenges associated with NPS use, considering the fast-evolving nature of these substances, or integration with existing addiction/drug services. III) Interagency collaboration between law enforcement, healthcare providers, community organizations, and government agencies to enhance treatment access and support. IV) Harm Reduction strategies, including mobile outreach units staffed with healthcare professionals to reach out to individuals in crisis and provide immediate intervention and support; needle exchange programs; and training for healthcare professionals.

Several potential factors may influence the future trends in NPS, OTC and POM use within the custodial setting, including NPS, OTC and POM availability in the local market, ease of concealment, perceived lower detection risk, or changes in policies. Looking at the current substance trends in the general population could help to promptly investigate future trends in prison settings. For instance, we started noting consumption of e-cigarettes liquid filled with SCRAs in 2015 in non-prison population (Castellanos and Gralnik, 2016; Trecki et al., 2015) and later this trend become popular in custodial settings too (Frinculescu et al., 2022). Currently there are concerns in the community around the inclusion of SCRAs in edibles such as gummy bears or cookies (EMCDDA, 2023) which could be become soon a new practice to smuggle and conceal such substance in prisons. Additionally, since May 2022 we have wtinessed the emergence of semi-synthetic cannabinoids in the European market. Semi-synthetic cannabinoids such as hexahydrocannabinol are likely that to be produced from cannabidiol extracted from low-THC cannabis. The effects of such substances in humans are unknown, and products delivering high doses are raising concerns (EMCDDA, 2023). We could also see more synthetic opioids becoming a popular in prison in the future.

4.5. Symptom trends and implications of NPS and POM/OTC use

The available literature presents significant challenges in defining trends in the misuse of these substances over the past two decades, particularly within both the general population and the incarcerated population.

A 2021 study, extrapolating data from the US National Survey on Drug Use and Health (NSDUH), revealed a striking 167% increase in NPS consumption among adults in the United States between 2007 and 2014, particularly notable among young White males aged 18–25 (Neicun et al., 2021). Another investigation, based on NSDUH data from 2009 to 2013, examined self-reported NPS use, indicating a notable rise in self-reported NPS consumption during this period, with psychedelic tryptamines, psychedelic phenethylamines, and synthetic cannabinoids being the most prevalent substances reported (Palamar et al., 2015).

Similarly, a study conducted in Sweden demonstrated an increase in NPS consumption from 2010 to 2016 (Helander et al., 2020). Numerous studies have corroborated a global trend over the past two decades showing an escalation in the prescription of gabapentinoids and consequent misuse, as well as associated fatalities (Chan et al., 2023; Benassayag Kaduri et al., 2024; Torrance et al., 2020). A retrospective analysis of Texas Medicaid data from 2012 to 2016 revealed that younger age, male gender, neuropathic pain diagnosis, and pregabalin use were significantly linked to higher rates of gabapentinoid misuse (Ibiloye et al., 2021).

An analogous trend has been observed with opioids, as their prevalence and misuse have surged in recent years, leading to a substantial rise in overdose cases and fatalities, particularly in the context of fentanyl use (Spencer et al., 2020; Bonar et al., 2020; Black et al., 2020; Dart et al., 2015; Han et al., 2022). Although the available epidemiological evidence on NPS use has expanded in recent years, our understanding of lifetime prevalence rates remains limited due to the scarcity of relevant population-based surveys with adequate sampling designs (Neicun et al., 2021).

These findings are notably incomplete as they overlook the incarcerated population. Consequently, it is impractical for us to evaluate trends and implications related to prescription/over-the-counter medications and NPS within this demographic, let alone identify symptomatic trends. Consequently, we can only speculate that trends in this population mirror those observed in the general population.

4.6. Limitations of the review

The prevalence of outcomes and psychiatric symptomatology associated with NPS, OTC/POM use/misuse was not reported in the majority of studies (N=21), limiting quantitative data extraction. The absence of the assessment of risks of bias due to the significant heterogeneity in study design and population characteristics, and the consequent impossibility to use valid intervention-related tools for bias risk assessment is an additional limitation. Other limitations may be related to publication bias, as studies that report negative or null associations often go unpublished. Furthermore, the use of NPS and POM/OTC might be underestimated/under recognized as not identified due to the challenges in detection. Indeed, most commonly misused designer drugs cannot be detected by routine hospital toxicological diagnostic facilities, especially in those cases characterized by an unclear and incomplete medical history. Lastly, this review only included studies published in English; however, non-English articles were screened and no relevant studies emerged.

5. Conclusion

SCRAs emerged as the most recorded class of NPS in the present study. Interestingly, several POM specifically opioids, gabapentinoids, antidepressants, e.g., bupropion, are described here. It was also found that the OTC anticholinergic drug scopolamine N- butylbromide was misused in custodial settings.

Studies describe mostly psychiatric/neurological symptoms, highlighting that severe symptomatology is possible, e.g. aggressive behaviours, alterations in the level of consciousness, seizures, hallucinations, and anxiety, etc.

The consumption of NPS and the misuse of OTC and POM in prisons/custodial settings is an emerging worldwide problem, due to their neuropsychiatric implications and other health-related challenges. Addressing substance misuse in prisons and custodial settings requires a holistic, multi-faceted approach. Prioritizing prevention, treatment, and rehabilitation over mere punitive measures is key. The integration of evidence-based programs, staff training, education of persons in custody education, and collaboration with external agencies can lead to healthier, safer correctional environments and better outcomes for released individuals. Raising awareness of the use and misuse of such substances in these settings is important from an early warning perspective for law enforcement and policy makers and to prompt medical staff to prescribe with caution substances that may be misused and monitor them carefully. It is important for custodial authorities, policymakers, and healthcare professionals to remain vigilant, adaptable, and informed about evolving trends in drug use within custodial settings. By staying proactive, authorities can develop effective strategies to minimize the harms associated with substance use and promote the overall well-being of individuals in custody.

Author contributions

C.S., S.F., V.G. M.G. conceived the idea of this paper; data were extracted by S.G., G.G., C.R., and C.C., whilst Mi.A., M.A. and P.M. supervised all stages of the process and were consulted to resolve any possible disagreement. C.S. and V.G. drafted the first version and revised it after contributions from M.G., S.F., Se.F., C.J.M., S.J.L., and G.A. All authors approved the final version. All authors have read and agreed to the published version of the manuscript.

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Declaration of Competing Interest

S.F. was a member of the UK Advisory Council on the Misuse of Drugs (ACMD; 2011–2019) and is currently a member of the EMA Advisory Board (Psychiatry). Se. F. is a member of the UK's Independent Advisory Panel on Deaths in Custody. M.G. has been a consultant and/or a speaker and/or has received research grants from Angelini, Doc Generici, Janssen-Cilag, Lundbeck, Otsuka, Pfiser, Servier, Recordati. C.J.M. is a member of the ACMD's Novel Psychoactive Substances and Technical Committees. C.S., V.G., M.A., Mi. A., S.G., G.G., d'A.G, D.C.F., C.R., C.C., P.M., G.A.: nothing to be declared.

Data Availability

No data was used for the research described in the article.

Appendix A

Apendix A
Findings related to the case report

	Authors	Type of study	Country	Population	Mean Age (years)	Gender (M/F)	PsychiatricAnamnesis	Toxicologic Anamnesis	Other drugs / substances detected	AEs
Scopolamine	Strano-Rossi et al., (2021)	Case report	Italy	N = 1	41	M	ND	Cannabis use	Benzodiazepines, quetiapine, mirtazapine, valproic acid	ND
Tapentadol	Carelli et al., (2021)	Case report	Italy	ND	39	M	ND	Drug abuse/ misuse	Clotiapine, Diazepam	Severe respiratory depression and fatal intoxication

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