New Psychoactive Substances (NPS) and Serotonin Syndrome onset: a Systematic Review

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ABSTRACT

The use of several new psychoactive substances (NPS) has become very popular and is posing global health risks. Chemically and pharmacologically diverse molecules are constantly emerging and are presenting with a wide range of clinical implications. Serotonin toxicity, and specifically Serotonin Syndrome (SS), might develop as a result of an over-activation of the serotoninergic system caused by several mechanisms resulting in a classic triad of altered mental status, neuromuscular effects, and autonomic hyperactivity.

In the present systematic review, we have investigated and summarized the available evidence related to the association between SS and NPS intake.

Three retrospective studies, two case series and five case reports were included in this systematic review; several NPS were found to be implicated in SS occurrence These include psychedelic phenethylamines, e.g. 2, 5-dimethoxy-4-iodophenethylamine (2C-I); 2-(4-Iodo-2,5-dimethoxyphenyl)- N-I[(2-methyoxyphenyl)methyl]ethanamine (25I-NBOMe); and 5-(2-aminopropyl)indole (5-IT); and synthetic cathinones, e.g. mephedrone; 3,4-methylenedioxypyrovalerone (MDPV); methylone; butylone; NRG3; alpha-methyltryptamine (AMT); methoxphenidine (MXP); and the antidepressant bupropion. Bupropion was here misused at high dosages and/or in combination with other licit/illicit serotonergic drugs. Whilst most substances were ingested orally, nasal insufflation (with both 5-IT and 2C-I) and sublingual administration of blotter paper (with 25I-NBOMe) were reported as well. Interestingly, the psychiatric history was negative for most subjects, apart from two cases.

Clinicians should be aware of NPS potential risks and the severe consequences of their recreational use, including SS. Also, due to their undetectability in routine and common drug screenings, the diagnostic challenges posed by NPS should not be underestimated during the treatment of such patients.

KEYWORDS: serotonin syndrome, new psychoactive substances, NPS, synthetic cathinones, phenethylamines, bupropion

Introduction

The serotoninergic, serotonergic, or serotonin syndrome (SS) is a clinical condition characterized by the classical triad of autonomic hyperactivity, neuromuscular abnormalities and changes in mental status (Boyer & Shannon, 2005). However, symptoms may range from a mild flu-like feeling to life-threatening symptoms (Boyer & Shannon, 2005; Francescangeli et al., 2019). Autonomic nervous system symptoms include tachycardia, diaphoresis, mydriasis, shivering, diarrhoea, hyperthermia, myoclonus, and hyperreflexia. Neuromuscular abnormalities, such as myoclonus, incoordination, hyperreflexia, tremors, and muscle rigidity; and mental status changes, such as psychomotor agitation, hypomania, and confusion are other signs and symptoms which might be typically reported. In severe and life-threatening cases, delirium, seizures, shock, coma, and death may also occur (Boyer & Shannon, 2005; Volpi-Abadie et al., 2019). Due to the extreme variability in its presentation, the prevalence of SS is likely to be larger than the formally identified and reported cases (Francescangeli et al., 2019; Volpi-Abadie et al., 2019).

SS is secondary to an overactivation of the serotoninergic system that may be caused by several mechanisms: (1) inhibition of serotonin reuptake; (2) reduction of serotonin metabolism; (3) increase of serotonin synthesis or release; (4) activation of serotoninergic receptors (Francescangeli et al., 2019). Although mechanisms underlying the SS onset are partially unknown, symptoms of serotonin toxicity seem to be mostly related to an activation of 5-hydroxytryptamine (5-HT)-2A receptors (Sun-Eldestein et al., 2008). This hypothesis is supported by the efficacy of 5-HT-2A antagonists (e.g., cyproheptadine) in the prevention of death from hyperpyrexia in animals and humans with serotoninergic intoxication (Boyer & Shannon, 2005; Isbister & Buckley, 2005). Other receptors, such as 5HT-1A, may play a role in the development of SS, but the evidence is unclear (Sun-Eldestein et al., 2008).

SS has been associated with serotoninergic drug toxicity due to intentional self-poisoning, unintentional drug-drug interactions, or drug toxicity at times occurring at therapeutic doses (Boyer & Shannon, 2005). The onset of the symptomatology is usually within 4-6 hours from the index drug ingestion (Little et al., 2018; Nelson et al., 2007), although a delayed onset of up to 72 hours has been reported (Little et al., 2018). Moreover, it may occur either after a single administration due to idiosyncratic effects or individual vulnerability, or in patients chronically treated with a serotoninergic agent (Nelson et al., 2007). Among prescribing drugs, antidepressants, especially in combination with another medication (or substance) that also raises serotonin levels, such as another antidepressant or Hypericum/St John's

wort, have been associated with increased risks of SS (Nelson et al., 2006; Francescangeli et al. 2019). In particular, the molecules typically reported are: 1) serotonin reuptake inhibitors (SSRIs), e.g. sertraline, citalopram, etc., which boost the neurotransmitter serotonin, block the serotonin reuptake pump, desensitize serotonin receptors, especially serotonin 1A receptors, and presumably increase serotonergic neurotransmission (Stahl, 2018); 2) serotonin noradrenalin reuptake inhibitors (SNRIs), e.g. venlafaxine and duloxetine, which boost neurotransmitters serotonin, norepinephrine/noradrenaline, and dopamine, block the serotonin reuptake pump, presumably increasing serotonergic neurotransmission, and block norepinephrine reuptake pump, hence presumably increasing noradrenergic neurotransmission. They possibly desensitize both serotonin 1A receptors and beta-adrenergic receptors. Also, since dopamine is inactivated by norepinephrine reuptake in the frontal cortex, which largely lacks dopamine transporters, they can increase dopamine neurotransmission in this part of the brain; finally, they weakly block dopamine reuptake pump and this may increase dopamine neurotransmission (Stahl, 2018); 3) monoamine oxidase inhibitors (MAOIs), e.g. tranylcypromine, which irreversably block mono-amino-oxidase (MAO) enzymes from breaking down norepinephrine, serotonin, and dopamine, thus presumably boosting noradrenergic, serotonergic, and dopaminergic neurotransmission (Stahl, 2018).

A range of prescribing opioid drugs are also linked with SS, especially when given in association with antidepressants. Proposed mechanisms for opioids' serotonergic action include both a weak serotonin reuptake inhibition and an increased release of intrasynaptic serotonin through inhibition of gamma amino butyric acidergic presynaptic inhibitory neurons on serotonin neurons. Synthetic piperidine opioids are considered pro serotonergic and include fentanyl, methadone, meperidine, dextromethorphan, and tramadol. Moreover, phenanthrene morphine analogues, i.e., oxycodone, hydromorphone, and buprenorphine do not act as serotonin uptake inhibitors, but may increase the intrasynaptic serotonin levels either through increased release of neurotransmitter or some unknown mechanism (Beakley et al., 2016; Francescangeli et al., 2019; Rastogi et al., 2011; Stahl., 2018).

New psychoactive substances (NPS) is an umbrella term that includes new synthetic and herbal drugs such as synthetic cannabinoids, opioids, hallucinogens, synthetic cathinones and other stimulants (Corazza and Prilutskaya, 2018; Schifano, 2018; Schifano et al., 2015, 2017, 2019). The mechanisms of action of the different molecules are often complex and not fully understood. However, many NPS classes interact with both 5HT receptors (e.g. 5HT2A) and serotonin reuptake transporters (SERT) (Liechti, 2015; Schifano, 2018;

Schifano et al., 2015, 2019). Hence, substances with a prevalent serotoninergic interaction may be at high risk to induce SS (Liechti, 2015). A previous review (Zaami et al., 2018) of fatalities associated with synthetic cathinones (SC) intake reported that deaths were mainly associated with symptoms of SS, such as hyperthermia, hypertension, cardiac arrest, delirium and more in general to the “classic” clinical presentation of SS. However, data on SS induced or associated with NPS intake has not been previously systematically collected. Therefore, the main aim of this systematic review was to identify and summarize the available evidence on the relationship between SS and NPS intake.

Materials and Methods

The systematic review was structured in accordance with PRISMA (Moher et al., 2015) and PROSPERO guidelines (Bernardo, 2017). The identified studies were assessed through title/abstract and full text screening against eligibility criteria, which include only original articles written in English reporting the manifestation of a picture attributable to a serotonin syndrome after NPS consumption and are considered in this systematic review. For a more thorough description of both the search engines having been used and the search strategy, please refer to the supplementary material.

Data synthesis strategy

Data were extracted by n=4 reviewers (SC, AM, AV and VC), while n=4 senior researchers (FS, MP, GM, MDG) supervised all stages of the process and were consulted to resolve any possible disagreement. The exclusion criteria for both selection phases were: 1) non-original research (e.g. review, commentary, editorial); 2) non full-text articles (e.g. meeting abstract); 3) language other than English; 4) animal/in vitro studies; 5) articles not dealing with misuse of selected NPS (synthetic cannabinoids, cathinones, phenethylamine, piperazines, tryptamines, new synthetic opioids, MXE, PCP-like drugs, new benzodiazepines); 6) articles dealing with syndromes different from SS. After removing duplicate articles (n = 40) from a total of 120 papers (PubMed = 65; Scopus = 49; WoS = 5; other sources = 1), the remaining 80 records were screened, and, of these, 66 were not relevant to the subject after reading title and abstract (e.g. animal/in vitro studies; articles not dealing with the misuse of NPS or with SS); 4 were not written in English; and 28 were non-original articles (e.g. reviews, metanalyses, commentaries, letters to the editor without data available, book chapters). Of the 14 full-text articles assessed for eligibility, three did not match the inclusion criteria for

our review ('not relevant to the subject reading title and abstract: animal/in vitro studies; articles not dealing with the misuse of NPS or with serotonin syndrome'), and 1 was not available. Finally, 10 articles were included for analysis (the operative method is summarised in Figure 1). The process was conducted individually by SC, AM, AV and CV, creating an Excel database and, for doubtful cases, the eligibility was discussed with GM, MP, SC and MDG. For dubious or missing results, the authors of the articles were contacted directly. All these research methods were approved by PROSPERO.

Results

Ten eligible articles, reviewing the prevalence of SS following the intake of an index misusing drug, were identified and included in this systematic review. All results are summarized in Table 1.

Data were collected mostly from the United States (US) (Bosak et al., 2013; Moss and Hendrickson, 2019; Murray et al., 2020; Sidlak et al., 2020; Umemura et al., 2015; Warrick et al., 2011) and in three European nations, specifically the Netherlands (Spoelder et al., 2019), France (Batisse et al., 2014; Chrétien et al., 2018) and Sweden (Bäckberg et al., 2014), during years 2011 - 2020. Studies retrieved were represented by five case reports (Bosak et al., 2013; Chrétien et al., 2018; Spoelder et al., 2019; Umemura et al., 2015; Warrick et al., 2011), three retrospective studies (Moss & Hendrickson, 2019; Murray et al., 2020; Sidlak et al., 2020) and two case series (Bäckberg et al., 2014; Batisse et al., 2014).

Substances identified included the following compounds (Table 2): α-methyltryptamine (AMT) (Chrétien et al., 2018); methoxphenidine (MXP) (Chrétien et al., 2018); several synthetic cathinones (Batisse et al., 2014; Warrick et al., 2011), e.g. mephedrone; 3,4-methylenedioxypyrovalerone (MDPV); methylone; butylone; NRG3; 2,5-dimethoxy-4-bromophenethylamine (2C-B) (Spoelder et al., 2019); other several phenetylamine derivatives, e.g. 2, 5-dimethoxy-4-iodophenethylamine (2C-I) (Bosak et al., 2013); 2-(4-Iodo-2,5-dimethoxyphenyl)- N-I[(2-methyoxyphenyl)methyl]ethanamine (25I-NBOMe) (Umemura et al., 2015); and 5-(2-aminopropyl)indole (5-IT) (Bäckberg et al., 2014). Moreover, the antidepressant drug bupropion, especially in association with alcohol (Umemura et al., 2015), marijuana (Umemura et al., 2015), ketamine (Bäckberg et al., 2014), and buprenorphine (Bäckberg et al., 2014), were found to be associated with several cases of

serotonin toxicity and SS (Moss et al., 2019; Murray et al., 2020; Sidlak et al., 2020) (Table 2).

Whilst most substances were ingested orally (Bäckberg et al., 2014; Chrétien et al., 2018; Sidlak et al., 2020; Warrick et al., 2011), nasal insufflation (for both 5-IT and 2C-I; Bäckberg et al., 2014; Bosak et al., 2013), and sublingual administration of blotter paper (for 25I-NBOMe; Umemura et al., 2015) were reported as well.

Interestingly, a psychiatric history was negative for most subjects apart from two cases. The first case was diagnosed with autism, where the subject was treated with methadone, loxapine and lorazepam (Chrétien et al., 2018), whilst the second case had a history of depression and a diagnosis of oppositional defiant disorder. In the latter case, the subject was treated with lithium and topiramate (Umemura et al., 2015). Two cases were recorded as occasional substance abusers (Bosak et al., 2013; Spoelder et al., 2019) (Table 1).

Most relevant acute symptoms recorded were related to sympathomimetic toxicity, and included tachypnoea, tachycardia, and hypertension; hyperreflexia/muscular rigidity, rhabdomyolysis, and seizures. Agitation and hallucinations were the most important psychiatric symptoms described. Severe serotoninergic toxicity included: urinary/renal and hepatic disfunctions; dysrhythmias and prolonged QTc interval; and toxic encephalopathy (Table 1). Two deaths from multiple organ failure were reported after the ingestion of 25I-NBOMe (Umemura et al., 2015) and methylone in combination with butylone (Warrick et al., 2011).

Overall, the treatment and management approach of the serotoninergic toxicity included here: hyperhydration; benzodiazepines and other anticonvulsants; and the anti-serotonin compound cyproheptadine. Where necessary, intubation, ventilation and haemodialysis were performed as well (Table 1).

Discussion

To the very best of our understanding, current data represent the first systematic review of cases of SS involving NPS reported in the literature. Although the sample is heterogeneous, cases are indicative of the severe consequences, including neurological complications, which might result from the use of NPS. Overall, those NPS presenting with a significant serotonergic activity should considered to be at risk of being associated with the occurrence of SS. Among recreational drugs, the overall full range of the well-known 179 psychedelic

phenethylamines, 3,4-MethyleneDioxyMethAmphetamine (MDMA)-like, derivatives (Schifano et al., 2015) have been most frequently associated with SS (Parrott, 2001). This is due to their action on the serotoninergic pathway increasing the activity of serotonin, dopamine, and norepinephrine (serotonin > dopamine and norepinephrine), and/or blocking its reuptake (Parrott, 2001; Parrott, 2002). Indeed, the NBOMe series NPS, which are direct derivatives of the substituted phenethylamine 2C-I family, may well be at risk of being associated with SS occurrence (Schifano et al., 2015; Schifano et al., 2017). Furthermore, one could observe signs and symptoms of an SS syndrome in clients having ingested either those synthetic cannabimimetics which possess levels of serotonergic activity (Zangani et al., 2020), or those synthetic cathinones which are displaying a prominent serotonergic activity (Schifano et al., 2020).

In line with these observations, most NPS recorded here were phenethylamine derivatives, such as 2C-B (Spoelder et al., 2019), 2C-I (Bosak et al., 2014), 5-IT (Bäckberg et al., 2014), and 25I-NBOMe (Umemura et al., 2015). Other compounds reported were the tryptamine AMT (Chrétien et al., 2018), and the following cathinones (Batisse et al., 2014; Warrick et al., 2011): mephedrone; MDPV; methylone; NRG3. All these molecules share the core structure with amphetamines, acting on the serotoninergic system, showing stimulant, entactogenic and hallucinogenic properties (Mercolini, 2019; Scherbaum et al., 2017; Schifano et al., 2017). Effects may vary according to the chemical structure of the molecule, e.g. the 2C-B (4-bromo-2,5-dimethoxyphenethylamine) and 2C-C (2,5-dimethoxy-4-chlorophenethylamine) are associated with intense visual hallucinations and synaesthesia, whilst the intake of benzofurans and MDMA-like drugs results in stimulant effects (Scherbaum et al., 2017). Several cases of intoxications described symptoms and side-effects, including hypertension, hyperthermia, convulsions, dissociation, hallucinations, respiratory deficits, liver and kidney failure, and deaths in cases of overdose (King, 2014; Mercolini, 2019; Scherbaum et al., 2017) (Table 2).

The 25X-NBOMe series include the 25I-NBOMe hallucinogen, which is a derivative of the substituted phenethylamine 2C-I family and which shows a high affinity at the 5-HT2A receptor level. Desired effects include mental and physical stimulation, increase in associative and creative thinking, increased awareness, spiritual experiences, and hallucinations. Several reports of related fatalities and hospitalizations have been recorded (Schifano et al., 2017) (Table 2).

Synthetic cathinones (SC) are amphetamine-like molecules derived from cathinone, a stimulant compound found in the khat plant, possessing pharmacological similarity to amphetamine and methamphetamine (Schifano et al., 2017). They appeared on the drug market in the mid-2000s and are generally believed to block the reuptake of norepinephrine, dopamine, and serotonin, with subtle structural variations that alter their chemical properties, potency, pharmacokinetics, and pharmacodynamics. For example, mephedrone and methylone are both serotonin and dopamine releasers, while MDPV is a dopamine selective uptake inhibitor thus presenting with a high abuse potential (Iversen et al., 2014; Schifano et al., 2017). Their sympathomimetic and/or amphetamine-like effects (Contrucci et al., 2019; Iversen et al., 2014; Schifano et al., 2017), include euphoria, alertness, increased energy, empathy, openness, mood enhancement, hallucinogenic experiences, and sexual arousal, observed within 30-45 min after administration and lasting 1-3 h. They can cause severe cardiovascular (e.g. tachycardia and hypertension), neurological, and psychiatric (anxiety, hallucinations, agitation, and aggression) side-effects (Assi et al., 2017; Mercolini, 2019; Scherbaum et al., 2017; Schifano, et al., 2015, 2017).

In 2019, more than 50 NPS have been detected for the first time by the EU (European Union) Early Warning System (EWS); SC were the most reported, detected and seized products, despite their early classification in prohibited substances lists (EMCDDA, 2020). The most common methods for SC consumption are insufflation (snorting/sniffing) or ingestion (‘bombing’: swallowing the powder wrapped in a cigarette paper; or mixed in a drink), but intramuscular and intravenous administrations have also been reported (Mercolini, 2019; Schifano et al., 2017). Cathinones’ use has been reported in practices including both injection and sexual/’chemsex’ parties (Batisse et al., 2014). A large proportion of users of SC report tolerance, dependence, and withdrawal symptoms (Schifano et al., 2017). A plethora of case reports concerning intoxications and fatalities due to SC consumption have been extensively and increasingly reported (Corazza and Prilutskaya, 2018; Mercolini, 2019; Scherbaum et al., 2017; Schifano, et al., 2015).

Bupropion is a monocyclic phenylethylamine antidepressant approved for the treatment of depression and smoking cessation by the Food and Drug Administration (FDA) (Murray, 2019). Its diversion has been recorded (with the following street names: ‘welbys’, ‘wellies’, ‘barnies’), especially with very-high dosages, in order to achieve an ‘amphetamine/cocaine-like high’ (Schifano, et al., 2015; Schifano et al., 2018; Schifano and Chiappini, 2018; Vento

et al., 2013). Furthermore, bupropion has been notified as an NPS in 2014 (EMCDDA, 2014). Literature studies (Moss and Hendrickson, 2019; Sidlak et al., 2020) included cases of serotonin toxicity involving bupropion overdose and recreational use. Although bupropion causes a non-selective inhibition of both noradrenaline and dopamine reuptake, as well as an antagonism on the neuronal nicotinic acetylcholine receptor (Schifano et al., 2018; Schifano and Chiappini, 2018; Vento et al., 2013), it has been previously implicated in several case reports of serotonin toxicity, either on its own or in combination with other serotonergic medications. This toxicity may be due to unknown mechanism which may include a toxicodynamic, downstream, indirect effect, or the effects of bupropion metabolites (Moss and Hendrickson, 2019). Alternatively, whilst acting on both norepinephrine and dopamine pathways, bupropion may lead to a sympathomimetic syndrome (e.g., tachycardia, diaphoresis, altered mental status) with dopaminergic neuromuscular effects (e.g., tremor, extrapyramidal effects), producing symptoms that are similar to that of serotonin toxicity but via a non-serotonin pathway (Schifano et al., 2018; Schifano and Chiappini, 2018; Vento et al., 2013). Furthermore, it is possible that bupropion increases concentrations of other types of serotonergic drugs, such as some SSRI antidepressants (e.g. sertraline and citalopram), but also of opioids (e.g. dextromethorphan, fentanyl, and tramadol; Contrucci et al., 2019; Moss and Hendrickson, 2019), or of other NPS such as mephedrone (Contrucci et al., 2019; Moss and Hendrickson, 2019).

AMT belongs to the monoamine alkaloids tryptamine group, derived from the amino acid tryptophan. Some naturally occurring tryptamine derivatives are identified in plants (e.g. N,N-dimethyltryptamine, DMT and 5-MeO-DMT), fungi (‘magic shrooms’, e.g. psilocin and psilocybin), or animal venoms (bufotenine) (Schifano et al., 2017), whilst synthetic tryptamines appeared on illicit drug markets only during the 1990s (Schifano et al., 2017). Tryptamines are serotonin receptor agonists and hence possess significant predominant hallucinogenic properties with the following effects: intensification of colours; distortion of body image; and visual hallucinations (Scherbaum et al., 2017; Schifano et al., 2017). All these elements might produce profound changes in sensory perception, mood, and thought (Corazza and Prilutskaya, 2018; Mercolini, 2019; Schifano, et al., 2015, 2017). Untoward effects include agitation, tachyarrhythmia, hyperpyrexia, serotonergic neurotoxicity, and death (Schifano et al., 2017).

The NPS MXP is structurally related to ketamine, with a greater intensity of effects and a longer half-life, marketed in 2013 since the banning of the similar compound methoxetamine (MXE) (Van Hout and Hearne, 2015). It acts as a N-methyl-D-aspartate (NMDA) antagonist and as an inhibitor of dopamine, serotonin and norepinephrine reuptake, with the highest affinity for dopamine transporter (DAT) > norepinephrine transporter (NET) > serotonin transporter (SERT) (Chrétien et al., 2018; Luethi et al., 2018; Schifano et al., 2015; Wallach et al., 2016; WHO, 2020). It presents with an action at the mu and delta opioid receptors as well (Schifano et al., 2015; Wallach et al., 2016; WHO, 2020). MXP shows euphoric, empathogenic, stimulant, and dissociative characteristics with altered sense of time and space, visual distortions and auditory hallucinations (Schifano et al., 2015; Van Hout and Hearne, 2015; Wallach et al., 2016). MXP might be highly addictive because of its ability to produce intense psychedelic and dissociative mind-altering effects both via the 5-HT2A and 5-HT2C receptors agonism activity and via N-methyl-D-aspartate receptor antagonism (Chrétien et al., 2018; Luethi et al., 2018; Van Hout and Hearne, 2015; Wallach et al., 2016). A range of serotonin syndrome signs/symptoms have been associated with both diphenidine/DND and MXP high dosage ingestion (Chrétien et al., 2018; Schifano et al., 2015; Wallach et al., 2016; WHO, 2020). Acute intoxication can lead to emergency department admissions or even death (WHO, 2020).

As recorded by Chrétien et al., 2018, the Internet has emerged as the new marketplace for NPS, playing a major role in providing information on acquisition, synthesis, identification, and substance use (Deluca et al., 2012). In fact, through the extensive monitoring of blogs/fora (e.g. Erowid, Bluelight), social media and other Internet resources (e.g. YouTube®), emerging trends of NPS may be identified and adequately described (Deluca et al., 2012; Orsolini et al., 2017). Furthermore, manufacturers, suppliers, retailers may all be web-based for the marketing or sale of psychoactives (Corazza and Prilutskaya, 2018; Karila et al., 2011; Orsolini et al., 2017), with customers being able to shop with relative anonymity in a 24-hr marketplace facilitated by the development of both anonymised illegal networks, e.g. the “Darknet”, and of electronic currencies (Corkery et al., 2017; Orsolini et al., 2017). Attracted by virtual reality and internet technologies, psychonauts' communities of NPS enthusiasts experiment with drugs with unknown compounds/combinations and then share NPS-related opinions, information, links, and experiences (Corkery et al., 2017; Orsolini et al., 2015; Scherbaum et al., 2017).

Users are unaware of the potential ill-health effects of NPS, which may translate into serious clinical situations which are beyond the SS here examined. Indeed, NPS intake may be typically associated with the imbalance of a range of neurotransmitter pathways/receptors, and consequently with the risk of medical and psychopathological disturbances. The occurrence of these disturbances has been related to (for a thorough review, see Schifano et al., 2015; Schifano et al., 2019):

a) increased central dopamine levels, associated with the intake of most of these substances, including novel psychedelic phenethylamines and synthetic cathinones; with the acute ingestion of these drugs, agitation, anxiety, paranoid ideation, aggression, together with tachycardia, hypertension, hyperthermia, angina pectoris, myocarditis, abdominal pain, rhabdomyolysis, and convulsions can be observed;

b) cannabinoid CB1 receptor activation, achieved with synthetic cannabimimetics. With these molecules, auditory/visual hallucinations, anxiety, paranoia, behavioural dyscontrol, mood swings, suicidal ideation, panic attacks, agitated/excited delirium, florid/acute transient psychosis have been described. A chronic synthetic cannabimimetics' (e.g., 'Spice') intake has been associated with the occurrence of 'spiceophrenia' (Papanti et al., 2013). Furthermore, typical acute medical untoward effects may include vomiting/nausea; hypertension and tachycardia; seizures, encephalopathy, coma; and stroke.

c) 5HT2A receptor activation, reported with NBOMes, some tryptamine derivatives, dextromethorphan and hallucinogenic plants. With these NPS, dysphoria, panic, paranoid feelings, flashbacks and hallucinogen-persisting perceptual disorder (HPPD) can observed. Agitation, tremor, tachycardia, hyperthermia, and rhabdomyolysis have been described as well;

d) antagonist activity at NMDA receptors, described with ketamine/phencyclidine-like dissociatives. Related anxiety, dissociation, depersonalisation, auditory/visual hallucinations, tachycardia, and risk of accidental injury issues have been identified;

e) k-opioid receptor activation, typically associated with *Salvia divinorum* intake; perceptual disturbances; psychosis; irritability and anxiety, can be observed as a result of the intake of these molecules.

NPS are at times being perceived as "non-lethal" recreational illicit substances, which give a false sense of security to the recreational user. Although NPS have been related to a high proportion of drug-poisoning deaths during the past fifteen years (Schifano et al., 2012; Corkery et al., 2020), in the present study only two cases of drug-related SS recorded a fatal

outcome, and both were the result of a multiple organ failure from 25I-NBOMe (Umemura et al., 2015) and Methylone and butylone (Warrick et al., 2011).
Other severe cases requiring long-term hospitalizations were presented here (Bosak et al., 2013; Chrétien et al., 2018; Spoelder et al., 2019). Symptoms might have been enhanced by the concomitant use of other both licit (e.g. dextromethorphan, methadone, etc.) and illicit (e.g. tetrahydrocannabinol/THC; other NPS) drugs (Bäckberg et al., 2014; Chrétien et al., 2018; Moss et al., 2019; Spoelder et al., 2019; Umemura et al., 2015). Interactions between metabolic pathways of cathinones, antidepressants, and other NPS have been reported in the literature. It has been hypothesized that these interactions are both pharmacokinetic (e.g. metabolism via cytochrome P450 enzymes and their inhibition) and pharmacodynamic (e.g. increasing the extracellular monoamine concentration by affecting reuptake transporters issues) (Contrucci et al., 2019).

Although there are no epidemiological studies highlighting the prevalence of SS in NPS users, according to Parrott (2002) the acute boost in serotonergic monoamine activity related to the intake of MDMA/ecstasy, and arguably with its derivatives (Schifano et al., 2017), can generate feelings of elation, emotional closeness, and sensory pleasure. The acute serotonergic overactivity is exacerbated by the clubs/raves' high ambient temperatures, overcrowding (aggregate toxicity), and use of other stimulant drugs. In these cases, mild versions of the serotonin syndrome often develop, when hyperthermia, mental confusion, and hyperkinesia predominate. Rest in a cooler environment generally reverses these issues, although the emergency departments toxidromes commonly encountered after ingestion of cathinones and phenethylamines include risk of developing a serotonin syndrome (Kronstrand et al., 2018).

The management and treatment of the SS recorded included here benzodiazepines (Bäckberg et al., 2014; Bosak et al., 2013; Chrétien et al., 2018; Moss et al., 2019; Murray et al., 2020; Sidlak et al., 2020; Spoelder et al., 2019; Umemura et al., 2015) which, given the complex/unknown pharmacology of the substances involved (and their lack of detectability), may be the agents of choice, despite the possible need of re-dosing and possible problems whilst in presence of alcohol (Schifano et al., 2017). Hyperthermia, due to its fatal potential, should be always aggressively treated, with the help of cooling measures and intravenous fluid administration for rhabdomyolysis concern. Appropriate sedation and assisted ventilation have also been used occasionally (Bäckberg et al., 2014; Bosak et al., 2013; Chrétien et al., 2018; Murray et al., 2020; Sidlak et al., 2020; Spoelder

et al., 2019; Umemura et al., 2015). Finally, despite reported in the occurrence of the SS (Schifano et al., 2015, 2017), the antagonist of serotonergic receptors cyproheptadine has not always been used for its management (Bosak et al., 2013).

In all recorded cases, drug screening tools were limited in their ability to detect NPS involved, except for Warrick et al., 2011, where confirmatory drug laboratory tests on both patient samples (both biological fluids and hair) and on the drug sample identified and detected the same substances (methylone and butylone). In most cases, standard drug screening, typically relying on enzyme-immuno assays, is limited in its ability to identify most NPS in blood or urine; due the high selectivity of this type of immunoassay, this is true also for both phenetylamines and cathinones, which could hypothetically be expected to cross-react with the substrate used for amphetamine immunoassays (Corazza and Prilutskaya, 2018). Confirmatory techniques such as gas chromatography/liquid chromatography and mass spectrometry approaches are more robust and reliable, but both are expensive and time-consuming and might not be applied in routine drug screenings in emergency departments or in psychiatry (Scherbaum et al., 2017). Identification of complex mixtures may require combined analytical analysis, availability of reference standards and high-quality specific libraries.

Conclusions

Despite the growing literature on NPS, the current knowledge about the clinical effects of their use is still limited. The present findings suggest NPS might be associated with potential severe complications, including SS and potential fatalities. Thus, due to the lack of scientific knowledge of these substances, especially safety data, the emergence of NPS is a challenge for medicine, for psychiatry and for the addiction treatment system. Physicians, but also people who use drugs, should be aware of the risks posed by NPS and their use, including their interaction with other psychoactive substances. Also, due to their undetectability with common drug screening tools, the diagnostic challenges posed by NPS should not be underestimated whilst treating such patients.

Declaration of interest

FS 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). JMC is a member of the ACMD’s Novel Psychoactive Substances and Technical Committees. NS: received

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Authors' contributions

FS, SC, JMC, and AG conceived the idea of this paper; data were extracted by SC and AM, whilst FS, MP, GM, MDG supervised all stages of the process and were consulted to resolve any possible disagreement. FS, SC, CZ and AM drafted the first version and revised it after contributions from JMC, NS, DA, FN and AG. All authors approved the final version.

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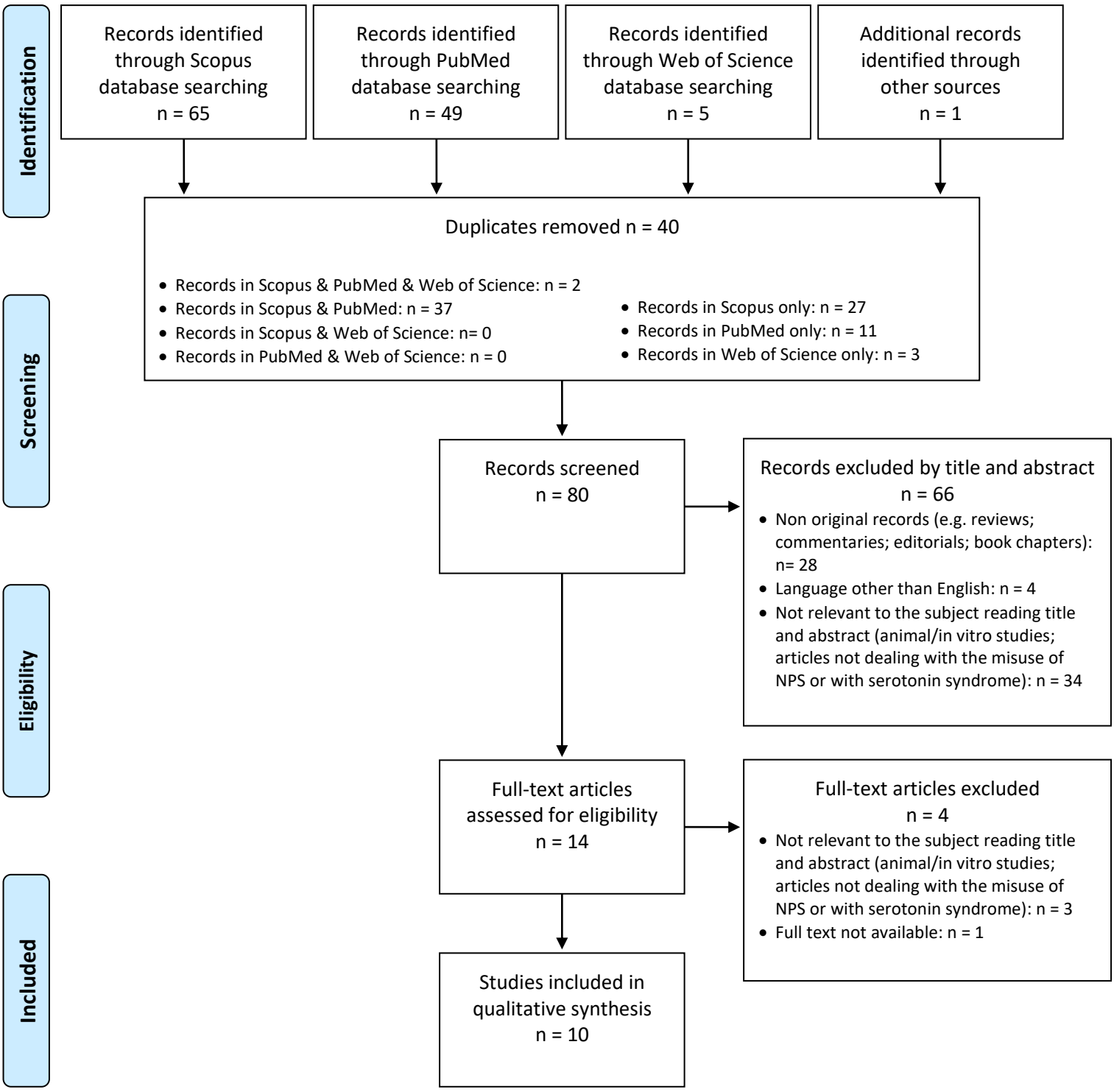
PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Table 1. Overview of literature cases of New Psychoactive Substances and Serotonin Syndrome: summary of the main findings

Study	Type of study (country)	Sample features (gender, age)	Medical/ Psychiatric history (if any)	Psychiatric therapy (if any)	NPS of interest (dosage, ROA)	Drugs/substances in combination (if any)	Clinical effects reported	Treatments reported	OUTCOME
Bäckberg et al., 2014	Case series (Sweden)	Observational case series of patients with admitted or suspected intake of NPS presenting to hospitals in Sweden in 2012, with N tot = 6 presenting with serotonin syndrome (PSS: 3 corresponding to severe or life-threatening symptoms)	Not specified	Not specified	5-IT (ROA nasal, oral)	6-APB; MDPV; alcohol; ethylphenidate; mephedrone; ecstasy; amphetamine; alprazolam; cocaine; desmethyldiazepam; 4-OH-midazolam; methoxetamine; ritalinic acid; oxazepam; temazepam; THC; buprenorphine; thiopental; pentobarbital	• Agitation (four patients) or CNS depression (two patients) and all but one had hyperthermia above 40 C on admittance • Sympathomimetic toxicity with tachypnea, tachycardia, hypertension • Rhabdomyolysis, hyperkalemia, increased serum creatinine level, increased muscle tone or rigidity	• Sedation with propofol and/or benzodiazepines • Where necessary, intubation, ventilation and hemodialysis were performed	• Not specified
Batisse et al., 2014	Case series (France)	Among 21 synthetic cathinones (SC) abuse notified to the Centre for Evaluation and Information on Drug Dependence and Addiction surveillance between 2011- 2012, N = 1 serotoninergic syndrome has been recorded	Not specified	Not specified	SC (dosage and ROA not specified)	Not specified	• Not specified	• Not specified	• Not specified
Bosak et al., 2013	Case report (US)	M, 19 yrs,	No significant past medical history and was not on any medications. He rarely consumed alcohol and had no history of another illicit drug use	None	2C-I (dosage not specified, ROA nasal)	None	• Recurrent generalized tonic–clonic seizures; tachycardia; hypertension; desaturation; GCS: 6; hyperthermia; muscular rigidity; spontaneous clonus; agitation; hallucinations	• Ventilation; naloxone (2 mg IV); midazolam (2,5 mg IV); lorazepam (2 mg IV); intubation; propofol • Due to concern of persistent rigidity and inability to exclude ongoing seizures, the patient received phenobarbital along with cyproheptadine. Despite the administration of phenobarbital and propofol, agitation persisted prompting	• The agitation and hallucinations resolved on hospital day 5 and the patient was discharged home on hospital day 6 • During the 2 weeks after discharge, the patient had episodes of forgetfulness, although at

								continuous infusions of fentanyl and midazolam	follow-up 2 months after discharge, the patient was back to his baseline
Chrétien et al., 2018	Case report (France)	M, 33 yrs	Autism	Methadone; loxapine; lorazepam	MXP (dosage not specified, ROA oral)	AMT	• Psychomotor agitation; hyperthermia; tachycardia; mydriasis; GCS: 10; T: 42 C • He developed hypercapnic acidosis, renal and hepatic dysfunction	• Supportive care was performed including mechanical ventilation with sedation, endovascular targeted temperature management, large hydration, hemodialysis, and blood transfusions • Dantrolene (100 mg) was administered at 24 hours after hospital admission to prevent a possible neuroleptic syndrome related to the recent treatment with loxapine.	• The patient was discharged from the resuscitation department after 16 days with good recovery
Moss et al., 2019	Retrospective study (US)	Among 1,010 cases of serotonin toxicity in the ToxIC Registry (2010-2016), N = 147 bupropion-related cases have been included	Not specified	Not specified	Bupropion (dosage and ROA not specified)	Dextromethorphan; lamotrigine; and tramadol	• Hyperreflexia/clonus/myoclonus; agitation; tachycardia; rigidity; seizures; hyperthermia; rhabdomyolysis; and death	• Benzodiazepines and, if necessary, intubation	• Not specified
Murray et al., 2020	Retrospective study (US)	Among 221 cases of serotonin toxicity in the ToxIC Registry (2014-2017) where bupropion was the single agent, N = 13 developed serotonin syndrome; M/F : 0.85; mean age 17 (15-25) yy	Not specified	Not specified	Bupropion (dosage and ROA not specified)	None	• Tachycardia; agitation; clonus; seizures; toxic psychosis; prolonged QTc; CNS depression; dystonia	• Benzodiazepines; anticonvulsants (other than benzodiazepines); and, if necessary, intubation	• Not specified
Sidlak et al., 2020	Retrospective study of bupropion overdoses during 2015–2017 (US)	Among the 18 bupropion overdoses recorded, N tot = 2 cases diagnosed with serotonin syndrome: M/F= 1, mean	Not specified	None	Bupropion (mean dosage 3,750 ± 2,250 mg; ROA oral)	None	• Tachycardia within 24 h of admission; hyperthermia; altered sensorium; agitation; diaphoresis; hyperreflexia; seizures • Toxic encephalopathy	• Benzodiazepines	• Not specified

		age 34,5 ± 12,5 yrs							
Spoelder et al., 2019	Case report (Netherlands)	M, 18 yrs	No medical history; previous occasional use of substances (cannabis; LSD; and alcohol) recorded	None	2C-B (dosage and ROA not specified)	THC	• Found at home unresponsive (GCS: 3); tachycardia; hypertension; anisocoria • After 1-day hospitalization in the ED: tonic seizures; urinary incontinence; hematemesis; T: 38.5 C; CK>10,000 IU/L; elevated troponins and transaminases; metabolic acidosis. Neuroimaging (CT and MRI) showed mild cerebral edema without signs of ischemia • After 5-days hospitalization in the ED the CT showed cerebral herniation	• Benzodiazepines • Levetiracetam (IV); sedation and intubation; hyperhydration with crystalloid solution; dexamethasone; and antibiotics (meningitis in DD) • Cerebral herniation required osmotherapy and then a bilateral decompression craniectomy	• Twelve months after discharge, the patient was in a minimally conscious state (PALOC score 5/8)
Umemura et al., 2015	Case report (US)	F, 17 yrs,	Depression; Oppositional defiant disorder; Headache	Lithium; Topiramate; Ibuprofen	25I-NBOMe (dosage not specified, ROA sublingual blotter paper)	Alcohol, THC	• Agitation; status epilepticus and hyperthermia (T= 41.9 C); tachycardia; oliguria; and unresponsiveness occurred within hours of 25I-NBOMe ingestion • Severe complications of the serotonin syndrome included rhabdomyolysis; metabolic acidosis; renal failure; and disseminated intravascular coagulation • The CT scan demonstrated subtle findings concerning for encephalopathic injury. The MRI demonstrated restricted diffusion in the cerebellum and posterior regions with T2 signal increased in both cerebral cortices and basal ganglia, consistent with extensive cerebral injury • Progressive cerebral edema resulted of combined injury from hypoxia, hyperthermia, and metabolic and perfusion derangements associated with serotonin syndrome and renal failure: brain dead on hospital day 7	• Intubation; lorazepam (2 mg IV); midazolam (5 mg IV); propofol; levetiracetam • Hemodialysis	• Death from acute intoxication resulting in status epilepticus; encephalopathy; disseminated intravascular coagulation; diffuse alveolar damage; acute kidney injury; and multiorgan system failure

Warrick et al., 2011	Case report (US)	F, 24yrs	History of psoriasis; she experimented with marijuana and cocaine in the past, but she was not a chronic abuser	Not specified	Methylone; butylone	None	• The patient presented to the emergency department, comatose, febrile, tachycardic, tachypneic, and hypertensive • On examination, she was diaphoretic, tremulous, hyperreflexic, and had sustained clonus	• Benzodiazepines (diazepam for apparent seizure activity; myoclonus was initially controlled by 2 mg of intravenous lorazepam followed by 32 mg of midazolam administered between 15 and 45 min post presentation • Supportive care included mechanical ventilation, temperature management, large hydration, and blood transfusions	• Ten hours post-admission, the patient developed pulseless electrical activity arrest from an unclear etiology. Spontaneous circulation returned within 90 s of CPR and 1 mg of epinephrine, but she required multiple pressors (norepinephrine, vasopressin, and dopamine) • Over the next 24 h,rs she developed ARDS and renal failure • She expired 48 hrs after presentation (according to the medical examiner, the cause of death was SS secondary to methylone and butylone.)

ARDS: Acute Respiratory Distress Syndrome; AMT: α-methyltryptamine; CK: Creatine Kinase; CNS: Central Nervous System; CT: computed tomography; DD: differential diagnosis; ED: Emergency Department; F: female; GCS: Glasgow Coma Scale; IV: Intra Venous; LSD: lysergic acid diethylamide; M: male; MDPV, methylenedioxypyrovalerone; MRI: Magnetic Resonance Imaging; MXP: Methoxphenidine; NPS: New Psychoactive substances; PALOC: Post-Acute Level Of Consciousness; PSS: Poisoning Severity Score; ROA: Route of Administration; SS: Serotonin Syndrome; T: temperature; ToxIC: Toxicology Investigators Consortium; US: United States; 2C-B: 2,5-dimethoxy-4-bromophenethylamine; 2C-I: 2, 5 dimethoxy-4-iodophenethylamine; 25I-NBOMe: 2-(4-Iodo-2,5-dimethoxyphenyl)-N-I[(2-methyoxyphenyl)methyl]ethanamine; 5-IT: 5-(2-aminopropyl)indole; 6-APB, 6-(2-aminopropyl)benzofuran.

DRUG	MECHANISM OF ACTION	RECREATIONAL USE	TOXICITY	REFERENCE
α-Methyltryptamine (AMT)	• It is a synthetic tryptamine and an indole analogue of amphetamine, both inducing the release and inhibiting the reuptake of monoamines, with stronger effects on the serotoninergic system • AMT also inhibits monoamine degradation	• Potent hallucinogen effects at doses above 30 mg	• Anxiety, muscle tightness, vomiting, hyperthermia, increase in blood pressure or respiratory rate, tachycardia, salivation, nausea, impaired coordination, terrifying hallucinations, nervousness, and restlessness • Deaths have been linked to acute AMT intoxication	Chrétien et al., 2018
Bupropion	• Synthetic cathinone, which acts through a dopaminergic, stimulant-like activity, and selective norepinephrine and dopamine reuptake inhibition	• Known in the street as 'welbys', 'wellies', 'dubs', or 'barnies', it might be misused up to 4,050 mg/day, roughly 14 times higher than the maximal therapeutic dosage, in order to achieve an 'amphetamine-like effects, including euphoria and enhanced motivation	• Irritability, agitation, tachycardia, cardiac toxicity, hallucinations, and seizures	Moss et al., 2019; Murray et al., 2020; Sidlak et al., 2020
Methoxphenidine (MXP)	• It is an arylcyclohexamine marketed in 2013 since the banning of the similar compound MXE, having greater intensity of effects and a longer half-life than ketamine • It acts as a NMDA antagonist and as an inhibitor of dopamine, serotonin and norepinephrine reuptake (DAT > NET > SERT • It appears to have an action on the mu and delta opioid receptors as well	• It is used as a recreational psychoactive substance with intense psychedelic and dissociative effects • It might be highly addictive	• Behavioural, emotional, motivational, cognitive and somatosensory and motoric changes, as well as cardiovascular effects including hypertension and tachycardia • At higher doses, hallucinations and out-of-body experiences, depersonalization, derealization, loss of ego boundaries, and, in some cases, delusions and paranoia can occur • Acute intoxication can lead to emergency department admissions or even death	Chrétien et al., 2018

Synthetic cathinones (SC), e.g. mephedrone; 3,4-methylenedioxypyrovalerone (MDPV); methylone; butylone; **NRG3**	• They inhibit dopamine and norepinephrine uptake resulting in stimulant effects	• Stimulating effects include: rush of intense pleasure; feeling happy, energetic and wanting to talk more; intense connection with music; restlessness; muscle tension (face and jaw); light-headedness; dizziness; distorted sense of time • Frequently used during 'Chem Sex Parties' in combination with other drugs such as methamphetamine, GBL/GHB, cocaine and sildenafil to enhance sexual experiences; and among young adults attending techno-alternative parties	• Headache, tachycardia, confusional states, rhabdomyolysis, renal failure or serotonin syndrome • Paranoia, auditory and visual hallucinatory experiences, agitation, anxiety, suicidal ideas, or suicidal attempt • Acute sexual behaviour disorder with hypersexuality, and violent behaviour	Batisse et al., 2014; Warrick et al., 2011
2,5-dimethoxy-4-bromophenethylamine (2C-B)	• It is a psychedelic phenylethylamine derivative with 5-HT2A, 5-HT2B, and 5-HT2C receptor partial agonism • Known as 'Nexus'/'Bees'/'Venus'/'Bromo Mescaline'/'BDMPEA'	• Psychedelic/psychostimulant-like effects, including euphoria; changes in perceptions (distances, colours, shapes, and lights) and different body feelings/surrounding	• Hypertension, tachycardia; mild to intense diarrhoea, nausea, and general gastrointestinal discomfort; headaches after coming down from large doses have been reported • At high doses (over 30–40 mg) severe hyperthermia and hypertension, and frightening hallucinations and paranoia might be experienced	Spoelder et al., 2019
2,5 dimethoxy-4-iodophenethylamine (2C-I)	• Phenethylamine derivative with agonist properties at the 5HT2 receptor, which is believed to be the aetiology of the hallucinogenic properties • It inhibits dopamine, serotonin, and norepinephrine re-uptake	• Lower doses resulting in stimulating effects, while higher doses are needed for hallucinogenic effects	• Neuropsychiatric manifestations include hallucinations, anxiety, agitation, and seizures • Hypertension, tachycardia, and respiratory depression	Bosak et al., 2014

	• 2C drugs are also agonists at the alpha-1 adrenergic receptor			
2-(4-Iodo-2,5-dimethoxyphenyl)-N-I[(2-methyoxyphenyl)methyl]ethanamine (25I-NBOMe)	• It is a derivative of the substituted phenethylamine 2C-I family, with a potent 5-HT2A receptor agonism	• Hallucinogenic stimulant that induces euphoria, psychomotor activation, and hallucinations	• Behavioural changes, mydriasis, agitation, seizures, hypertension, tachycardia, pyrexia, mydriasis, acute kidney injury, metabolic acidosis, leukocytosis, elevated transaminases, and rhabdomyolysis • Death	Umemura et al., 2015
5-(2-aminopropyl)indole (5-IT)	• A synthetic indole and phenethylamine derivative analogue of amphetamine	• Stimulatory effects provoking a psychedelic/hallucinogenic response	• Agitation, hallucinations, hypertension, hyperthermia, myoclonus, muscle rigidity, arrhythmias, seizures, rhabdomyolysis, and/or renal failure • Death	Bäckberg et al., 2014

Table 2. Overview of the New Psychoactive Substances (NPS) associated with Serotonin Syndrome recorded by the studies collected in the systematic review

DAT: dopamine transporter; MXE: Methoxetamine; NET: norepinephrine transporter; NMDA: N-methyl-D-aspartate; SERT: serotonin transporter; 5HT: serotonin.

Supplementary material

Systematic review procedures

A systematic electronic search was performed from the 13th of September 2020 until the 09th of November 2020 on the following scientific search engines: PubMed, Scopus, and Web of Science (WoS). The following search strategies were used, respectively in: *PubMed:* ("Synthetic cannabinoids" OR "Cathinones" OR "Phenethylamine" OR "Piperazines" OR "Tryptamines" OR "New Synthetic Opioids" OR MXE OR "PCP-like drugs" OR "New benzodiazepines") AND ("Serotonin Syndrome" OR "serotonin Toxidrome") NOT Review NOT (animal OR rat OR mouse); in *Scopus:* (TITLE-ABS-KEY ("Synthetic cannabinoids") OR TITLE-ABS-KEY ("Cathinones") OR TITLE-ABS-KEY (“Phenethylamine") OR TITLE-ABS-KEY ("Piperazines") OR TITLE-ABS-KEY ("Tryptamines") OR TITLE-ABS-KEY ("New Synthetic Opioids") OR TITLE-ABS-KEY (mxe) OR TITLE-ABS-KEY ("PCP-like drugs") OR TITLE-ABS-KEY ("New benzodiazepines") AND TITLE-ABS-KEY ("Serotonin Syndrome") OR TITLE-ABS-KEY ("serotonin Toxidrome") AND NOT TITLE-ABS-KEY (review) AND NOT TITLE-ABS-KEY (animal) OR TITLE-ABS-KEY (rat) OR TITLE-ABS-KEY (mouse)); and *WoS:* (("Synthetic cannabinoids" OR "Cathinones" OR "Phenethylamine" OR "Piperazines" OR "Tryptamines" OR "New Synthetic Opioids" OR MXE OR "PCP-like drugs" OR "New benzodiazepines") AND ("Serotonin Syndrome" OR "serotonin Toxidrome") NOT Review NOT (animal OR rat OR mouse)).