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REVIEW

The use of new psychoactive substances (NPS) in young people and their role in mental health care: a systematic review

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ABSTRACT

Introduction: Over the past 10 years, a large number of New Psychoactive Substances (NPS) have entered the recreational drug scenario. NPS intake has been associated with health-related risks, and especially so for vulnerable populations such as the youngsters. Currently, most knowledge on the NPS health effects is learnt from both a range of users' reports, made available through the psychonauts' web fora, and from the few published, related toxicity, clinical observations.

Areas covered: This paper aims at providing an overview of NPS effects on youngsters' mental health, whilst performing a systematic review of the current related knowledge.

Expert opinion: NPS consumption poses serious health risks, due to both a range of unpredictable clinical pharmacological properties and the typical concomitant use of other psychoactive molecules; overall, this can lead to near misses and fatalities. In comparison with adults, the central nervous system of children/adolescents may be more vulnerable to the activity of these molecules, hence raising even further the levels of health-related concerns. More research is needed to provide evidence of both short- and long-term effects of NPS, related health risks, and their addiction potential.

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NPS; novel psychoactive substances; 'legal highs'; mental health; youngsters

1. Introduction

Over the last decade, the emergence of a range of New Psychoactive Substances (NPS) has progressively changed the landscape [1] of the drug market, which has shifted with the raising use of the web from a 'street' to a 'virtual'/online one [2,3]. NPS include synthetic cannabinoids, cathinone derivatives, psychedelic phenethylamines, novel stimulants, synthetic opioids, tryptamine derivatives, phencyclidine-like dissociatives, piperazines, Gamma-AminoButyric Acid (GABA) -A/B receptor agonists, a range of prescribed medications (e.g. benzodiazepine derivatives; methylphenidate look-alikes; and fentanyl analogues), psychoactive plants/herbs, and a large series of image and performance enhancing drugs [1]. Since the United Nations Office on Drugs and Crime (UNODC) monitoring in 2009, NPS have been emerging every year at an average rate of about one substance per week [4–6]. Worldwide, synthetic cannabinoids and synthetic cathinones represent the largest groups of NPS being monitored [4,7,8]. Overall, users are typically attracted to NPS due to: curiosity and diffusion of social media users' experiences; easy availability/affordability from online drug shops; legality; intense psychoactive effects and likely lack of detection in routine drug screenings [6,9,10]. Interestingly, drivers for NPS use among students from a University in Northern Ethiopia appeared to be not only the easy access to NPS and prior experiences with substances, but also interpersonal factors, including detachment from family and difficulties in socialization; environmental factors such as limited recreational alternatives; and an unsatisfactory academic performance [11].

Due to the rapid life cycle of these substances, current health professionals' NPS technical understanding is a reason of concern. In recruiting 3,551 young people and health professionals to ask about their NPS knowledge, the European-wide RedNet Project found that the 69% of health professionals possessed levels of '*good/very good*' access to NPS information, although for some 16% of them considered their knowledge '*basic/essential*' or even '*insufficient*' [10,12–14]. Investigating the experiences and attitudes of adolescents/young adults toward NPS in a sample of over 12,000 young people (aged 15–24 years) across the 27 European Union (EU) member states, a variable rate of NPS intake, ranging from 16% in Ireland to 0.8–1.6% in Italy, Finland and Greece was identified [15]. Most NPS users appeared to be young (aged 15–24), males, and from urban areas [16–19]. In the UK, 2.6% of young people (aged 16–24) reported having used NPS in the last year [16]. Conversely, there are suggestions of a recently (from 2009 to 2013) increase in NPS use among both European and American young users [17,18]. With the help of both an online survey and a telephone interview, a UK-based specialist drug charity recently assessed the levels of NPS use in some 1,604-young people aged under 25, finding a lifetime prevalence of NPS use of around 66%, being synthetic cannabinoids the most commonly reported NPS [20–22]. Prior to ingesting an NPS, most youngsters had researched on these molecules from a range of

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Article Highlights

- Over the last decade, a growing number of NPS has been identified. They include a range of substances which are being used for recreational purposes. The large availability and easy access to NPS through both rogue websites and the 'deep web' make them popular among vulnerable clients, including young people and those with a history of drug abuse and/or mental health issues. Synthetic cannabinoids, central nervous system stimulants (e.g. cathinones), phenethylamines, and dissociatives account for most NPS being identified. Moreover, NPS may be self-administered in combination with remaining recreational drugs such as alcohol, cocaine or opioids.
- NPS-related clinical toxidromes differ according to the type of NPS ingested and range from sympathomimetic effects, euphoria, and agitation to respiratory depression. Fatalities have been recorded as well.
- High levels of NPS use are being identified in people diagnosed with psychotic; personality; or bipolar disorders.
- Unlike remaining recreational drugs, e.g. cocaine and 3,4-methylenedioxymethamphetamine (MDMA; ecstasy), NPS are typically going undetected. Hence, the provision of targeted clinical treatments to counteract toxicity and overdose may be problematic.
- Health-care professionals, and especially so child and adolescent psychiatrists, should be aware of new trends in drug scenarios so that they will be able to better identify possible NPS-related psychiatric symptoms.

sources, including YouTube®, pro-drug websites and user-driven educational/harm-reduction fora such as Erowid or Bluelight, both providing advice on dosage, typical psychoactive effects, and best possible drug combinations [14]. Even though are being perceived as safer compared with traditional drugs of abuse, NPS intake has been associated with adverse consequences, including risk of acute poisoning/death, suicide/self-harm, homelessness, offending, poor physical health and social problems [23,24]. NPS ingestion is described as particularly detrimental in psychiatric clients [25–32].

1.1. NPS and the youngsters; prevalence issues

Some London area, questionnaire-based, school surveys, carried out in subjects aged 15–18 years-old identified prevalence rates of NPS use ranging from 1.1% to 8% [33,34]. Conversely, an Australian questionnaire-based survey recruiting 682 subjects aged 18–35 years-old identified a relatively high (17.6%) lifetime use of NPS, mostly synthetic cannabinoids [35]. Interestingly, the prevalence of NPS (mainly synthetic cannabinoids) but also of cannabis and cocaine intake was significantly higher in a psychiatric sample of Italian young adults (aged 18–26 years-old) compared with a healthy population, where alcohol misuse and binge drinking behavior were more prevalent [36]. Moreover, NPS availability and knowledge seemed to be significantly higher among healthy Italian young adults from urban areas and mostly related to mephedrone [37]. Finally, the actual NPS intake was strongly related with binge drinking and reported by 4.7% of the sample, with mephedrone, synthetic cannabinoids, and Salvia divinorum being the most popular NPS [37].

1.2. Epidemiology of NPS use in young clubbers' sub-populations

A pilot study aimed at describing drug, including NPS, intake levels in a population of young adults (18–30 years-old; n = 273 subjects) attending five nightclubs in Rome through a self-reported questionnaire. The study identified a lifetime recreational drugs, including NPS, use in the 78% of the sample, with the most popular molecules including amyl nitrite (45%), synthetic cannabinoids (35%), lysergic acid diethylamide (LSD) (24%), mephedrone (18.8%), ketamine (18%), gamma-hydroxybutyrate (GHB) (10.2%), psilocybin (4%), and Salvia divinorum (3.2%) [38]. A survey-based study evaluating 682 adults (aged 18–25 years) entering electronic dance music events in New York City reported a lifetime use of any NPS in 35.1% of participants [39]. Synthetic cannabinoids were the most prevalent NPS reported (16.3%), followed by psychedelic phenethylamines (14.7%), synthetic cathinones (6.9%), other psychedelics (6.6%), tryptamines (5.1%) and dissociatives (4.3%) [38]. Similarly, apart from the methylenedioxymethamphetamine (MDMA), butylone and methylone among phenethylamines, were, respectively, identified in 47.9% and 10.4% of hair samples from 679 nightclub/festival-attending young subjects (aged 18–25) in New York City [40]. A survey-based study recruiting 679 American young adults (aged 18–25) entering electronic dance music parties evaluated ecstasy/MDMA vs non-ecstasy users [41]. Ecstasy users were more likely to report use of NPS (e.g. psychedelic phenethylamines and synthetic cathinones) and/or remaining unknown drugs (powders or liquids) compared to non-ecstasy users [42]. To profile mephedrone and synthetic cannabinoids' users, a US questionnaire-based survey carried out by Kelly et al. [43] recruited 18–40 years-old adults (n = 1,740) attending a range of night club venues in New York City. Latinos and younger adults seemed to be more likely to use synthetic cannabinoids, although the use of a variety of other substances, including alcohol, energy drink, club, and prescription drugs resulted to be quite prevalent [43].

1.3. NPS use amongst youngsters; web-based surveys/studies

An online survey recruiting a sample aged 13 to 30-years-old (www.thestudentroom.co.uk) identified large levels of lifetime prevalence (31%) of NPS use, with mephedrone (41%), Salvia divinorum (20%) and synthetic cannabinoids (11%) having been the most commonly reported NPS [12]. Finally, a non-participant netnographic qualitative study, collecting data from a list of cyber-drug/psychonauts' communities, reported that NPS use was mainly carried out by adolescents and young adults (aged 15–35 years) [13].

In the NPS acute/medium/long-term toxicity effect-related literature, there is a severe lack of pre-clinical studies, animal testing data, and clinical trials. Conversely, typical sources of information include the web fora psychonauts' self-reports; the self-reported surveys focusing on sub-populations of NPS users [44]; the case reports/series' anecdotal descriptions; and, the limited number of poison information services and emergency departments (ED) reports [45]. The rapid rate with which NPS appear, together with the uncertainties over their actual 'branding' and composition, pose substantial challenges for mental health-care providers [1,46], and especially so for child and adolescent mental health workers [7,13,14,47,48].

1.4. NPS-related fatalities in youngsters

In a UK-based study, the number of fatalities associated with NPS has risen in recent years from 10 in 2009 to 67 deaths in 2015 [49]. Recent research focussed on UK mephedrone fatalities in a sample of individuals aged 16–24 years at the time of death. Some 30 cases (with a mean age of 20-years old), mostly presenting with a history of drug use (85%), were identified [50]. Furthermore, all (n = 12) fatalities directly or indirectly related to misusing drugs registered in Ibiza from January to September 2015 were analyzed. Most (9 out of 12) cases were males, with a mean age of 30.5 years, and two victims of 18 years-old were reported as well [51].

1.5. Aims

Given the need and relevance of obtaining information and data concerning the role of NPS in mental health, and particularly amongst the vulnerable group of youngsters, a systematic review was here performed. We aimed at better understanding how the different NPS may influence/determine a range of mental health consequences.

2. Materials and methods

A systematic electronic search including original papers up to August 2019 was carried out by using the Pubmed/Medline database. The information was gathered in accordance with the PRISMA guidelines (http://www.prisma-statement.org/PRISMAStatement/Default.aspx.). LO and SC combined the search strategy of free text terms and exploded a range of MESH headings relating to the topics of youngsters' mental health and New/novel Psychoactive Substances. The search terms 'new psychoactive substances' and 'NPS' were cross-referenced with the terms 'Mental Health disorders', 'Youngsters', 'Adolescence', 'Young'; and major categories of mental illnesses, such as 'Anxiety Disorders', 'Mood Disorders', 'Bipolar Disorder', 'Depressive disorder', 'Schizophrenia', 'Psychotic Disorders', 'Dementia', 'Cognitive disorders', 'Eating Disorders', 'Sleep disorders' and 'Attention-Deficit Hyperactivity Disorder'. Thus, in order to retrieve the articles that were most relevant to our research question the following search string was applied: ((New psychoactive substances [Title/Abstract]) OR (Novel psychoactive substances[Title/Abstract])) OR (NPS [Title/Abstract]) AND (Mental Health disorders [Title/Abstract]) OR (Anxiety [Title/Abstract]) OR (Mood Disorders [Title/Abstract]) OR (Bipolar Disorder [Title/Abstract]) OR (Depression [Title/Abstract]) OR (Schizophrenia [Title/Abstract]) OR (Psychosis [Title/Abstract]) OR (Dementia [Title/Abstract]) OR (Cognitive disorders [Title/Abstract]) OR (Eating Disorders [Title/Abstract]) OR (Sleep disorders [Title/Abstract]) OR (Attention-Deficit Hyperactivity Disorder [Title/Abstract]) AND (Youngsters [Title/Abstract] OR Adolescence [Title/Abstract] OR Young [Title/Abstract])). All studies were initially screened by title and abstract to ensure that only the relevant ones were included. Furthermore, a search strategy by using specific NPS categories (i.e. synthetic cannabinoids, synthetic cathinones, synthetic phenethylamines, etc.) combined with the following terms 'Adolescence'/'Adolescent'/'Young'/'Youngsters'/'Mental Health' was here carried out as well. The above-mentioned search strategies were eventually screened with the use of the PubMed filter 'Adolescent: 13–18 years old'. Secondary searches were performed using the reference list of included articles and relevant systematic reviews. All published articles, without time and/or language restrictions were selected.

To be included in the present overview, studies had to meet the following criteria: a) being a peer-reviewed study; b) providing at least an abstract with full results published in English; and c) investigating a range of features pertaining to youngsters' mental health issues associated with prior/current NPS intake; d) human studies. As only limited levels of information were available, non-systematic and systematic reviews; case-series; and case-reports were here considered as well. Studies evaluating only epidemiological data and/or toxicological (i.e. intoxication, fatalities) data without considering/reporting data on psychopathological features and/or psychiatric disorders and/or mental health amongst youngsters were excluded from the present review.

After applying the age filter for each search strategy performed, a total of 428 results were identified (Figure 1). However, some 317 papers were excluded for a range of reasons, including: 74 were duplicates; 225 were not consistent with the inclusion criteria and/or with the topic of the research; 9 referred to animal studies; and for 9 papers the full-text was not made available, leaving a total of 111 papers to be evaluated. After removal of those 87 papers which did not provide a satisfactory range of information; and/or which did not specifically focus on youngsters' mental health; we were left with a total of 24 papers to be considered for the present review (see Table 1). To better investigate the role of the specific NPS classes and their effects on youngsters' mental health, the literature results were presented as either referring to the whole NPS category or to specific NPS classes. However, because of the limited levels of the available literature, the mental health issues referring to only two NPS categories, e.g. synthetic cannabinoids and synthetic cathinones were here considered. Data extraction was independently carried out by LO and SC; disagreements were resolved by discussion and consensus with a third member of the team (DP). Data were collected using an ad-hoc developed data extraction spreadsheet.

3. Results

3.1. Use of NPS; mental health issues; vulnerable sub-populations

A study by Martinotti et al. [36] compared the prevalence of NPS intake between a population of healthy Italian young adults (n = 2,615; aged 18–26-years old) and a psychiatric patient sample (n = 206). They demonstrated that NPS intake (mainly synthetic cannabinoids) was significantly higher amongst the psychotic and bipolar disorder patients. The authors concluded that NPS intake may be a likely factor to facilitate the occurrence of a full-blown development of a psychiatric disorder; alternatively, psychiatric patients may be more prone to approach NPS compounds because these

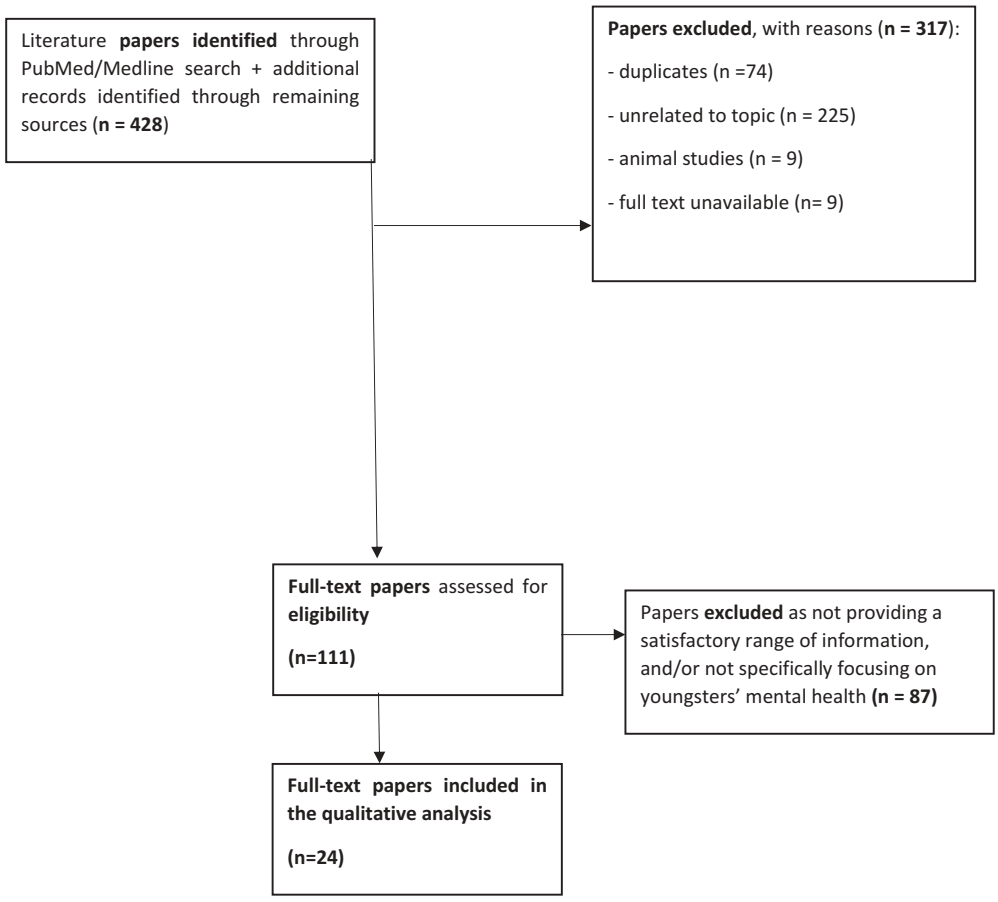

Figure 1. Selection of retrieved studies.

molecules are being perceived as 'legal' self-medicating agents [36]. In Japan, a multicentre retrospective survey of NPS products' poisoning events emphasized the involvement of youngsters; data were relating to 589 patients from 85 emergency facilities. Indeed, most patients were male (89.6%) and young (median age: 30 years; age range: 15–67 years-old). Amongst those hospitalized, approximately 5.3% of patients reported psychosis (hallucinations and delusions), 11% anxiety, 27.3% agitation and irritability; and 1.9% panic attacks [52]. A retrospective review of 388 electronic discharge letters relating to patients released from the Royal Edinburgh Hospital general adult psychiatric wards was carried out [53]. NPS were identified in 22.2% of admissions, determining psychiatric symptoms in 59.3% of the sample. When compared with non-NPS users (mean age 42.5 years old), NPS (mostly synthetic cannabinoids) users appeared to be younger (mean age: 36.1), males and more likely to present with a forensic history. Furthermore, the diagnosis of drug-induced psychosis was significantly more likely in NPS, vs non-NPS, users ($p < .001$; OR = 18.7, 95% CI 8.1 to 43.0) [53]. A multicentre observational study investigated the prevalence of NPS intake in a youngsters' (aged 18–26 years) Italian psychiatric sample (n = 617) [53]. About 8.2% (n = 55) of the subjects had ingested NPS at least once in their lifetime, whilst 2.2% (n = 15) had consumed one, or more, NPS over the previous 3 months. Most popular NPS were synthetic cannabinoids (4.5%; n = 30 subjects), and the three most represented psychiatric diagnoses included bipolar (23.1%; n = 15), personality (11.8%; n = 13), and schizophrenia/psychotic-related disorders (11.6%; n = 13) [54]. The mental health issues associated with the use of NPS in a sample of 90, mainly <30 years-old, users admitted to the Ibiza Can Misses Hospital Psychiatric Unit were formally assessed with the help of a range of psychometric scales. Most cases were characterized by poly-substance use (67%), whilst reporting a previous psychiatric history. Both positive (e.g. delusions and hallucinations) symptoms and hostility/aggression issues were frequent among tetrahydrocannabinol (THC) users, whilst anxiety symptoms were more prevalent in the group of sedatives' users [55]. Finally, a survey-based study was carried out to obtain information on the prevalence of 'drunkorexia' (e.g. self-imposed weight control measures combined with alcohol abuse) combined with drug, including NPS, intake in an Italian youngster (aged 18–26) sample (n = 4,275). A significant correlation was described between food restriction, binge drinking behavior, use of cocaine, and NPS use [41].

3.2. Use of synthetic cannabinoids; mental health issues and youngsters

A large collection of anecdotal reports of mental health issues associated with synthetic cannabinoids (SC; 'Spice') intake was here identified. Many psychiatric symptoms were described; although they were typically resembling

Table 1. Literature overview of NPS and mental health issues in the youngsters.

Author(s), year of publication	Sample features	Type of study	Setting	Substances	Outcomes
Martinotti et al., 2014 [36]	206 psychiatric patients and 2,615 healthy subjects (18–26 yy)	Questionnaire-based multicentric survey	Italy	NPS	• Alcohol consumption is more frequent in the healthy young population vs psychiatric young people (79.5% vs 70.7%; $p < .003$) • Cocaine and NPS use is significantly more common amongst psychiatric patients (cocaine 8.7% vs 4.6%; $p = .002$) (NPS 9.8% vs 3%; $p < .001$)
Lupi et al., 2017 [41]	4,275 healthy subjects (18–26 yy)	Questionnaire-based survey	Italy	Alcohol and NPS	• Significant correlation between drunkorexic attitudes and binge drinking behaviors ($p < .01$), use of cocaine ($p < .01$), and NPS use ($p < .01$)
Kamijo et al., 2016 [52]	589 patients coming from 85 emergency facilities	Multicenter retrospective survey of poisoning after consumption of products containing NPS	Japan	NPS	• 89.6% were male and young (median age, 30 years) • 88% inhaled NPS contained in herbal products (80.5%) • 6.9% reported violence, 4.9% traffic accidents, and 1.1% self-injury and/or suicidal attempts • 17.5% rhabdomyolysis, 12.4% liver injury, 9% acute kidney injury and 1.9% physical injury • Synthetic cannabinoids and synthetic cathinones detected only in the blood of 5 patients
Stanley et al., 2016 [53]	483 inpatients on general adult psychiatric wards (18–65 yy)	Cohort study	UK (Scottish city)	NPS	• 22.2% NPS use, contributing to psychiatric symptoms in 59.3% of cases • NPS users (vs not-NPS users) are younger ($p < .01$), male ($p < .001$) and more likely to have a forensic history ($p < .001$) • Drug-induced psychosis significantly higher amongst NPS-users ($p < .001$; OR = 18.7) • Depression significantly less likely amongst NPS users ($p < .005$; OR = 0.133) • Cannabis use significantly more likely in NPS users ($p < .001$; OR = 4.2)
Acciavatti et al., 2017 [54]	617 psychiatric patients (18–26 yy)	Multicenter-observational study	Italy (different cities)	NPS	• 8.2% declared to have used NPS at least once • 2.2% had consumed NPS in the previous 3 months • Bipolar disorder (23.1%), personality disorder (11.8%), and schizophrenia and related disorders (11.6%) were the most frequently associated diagnoses
Martinotti et al., 2017 [55]	90 young NPS users admitted in the Psychiatric Unit	Questionnaire-based survey	Ibiza	All substances, including NPS	• Polydrug abuse was reported by 67.4% of the sample; the sample was grouped by the main preferred substance in THC-, stimulants-, and depressors-users • Most patients reported a previous psychiatric history • Positive symptoms resulted to be higher among THC-users ($P < .05$). Anxiety evaluated by SCL-90 was prevalent in the group of Depressors-users ($P < .05$). The scores of MOAS and SCL-90 subscale for hostility/aggression resulted to be significantly ($P < .01$) greater in the THC-users group
Vearrier and Osterhoudt, 2010 [56]	A young adolescent (17 yy)	Case-report	USA	Synthetic cannabinoids	• Visual hallucinations, restless, anxious • Tachycardia, hypertension, diaphoresis, hypokalemia
Benford and Caplan, 2011 [57]	1 adolescent (20 yy)	Case-report	USA	Synthetic cannabinoids	• Anxiety, paranoia, visual and auditory hallucinations

(*Continued*)

Table 1. (Continued).

Author(s), year of publication	Sample features	Type of study	Setting	Substances	Outcomes
Castellanos et al 2011 [58]	11 subjects (15–19 yy)	Case-series	USA	Synthetic cannabinoids	• Hallucinations, difficulty thinking clearly, confusion, sedation, somnolence, disorganization or thought blocking, halting/ nonsensical speech, alogia, memory changes/problems, amnesia, increased focus, internal unrest, agitation, aggression, excitability, restlessness, decreased activity, anger, sadness, odd/flat affect, delusion, paranoid thinking, psychomotor retardation • Tachycardia, hypertension, conjunctival injection, nausea/ vomiting, xerostomia, tremors, numbness, tingling, lightheadedness, dizziness, seizures, pallor, tinnitus, diaphoresis
Every-Palmer, 2011 [59]	15 subjects (early twenties to mid-forties, mean 34 yy) with severe mental illness	Exploratory study	New Zealand	Synthetic cannabinoids	• Pronounced anxiety, florid psychosis with aggression (one subject), other psychotic symptoms (not specified)
Hurst et al., 2011 [60]	10 young adults (21–25 yy)	Case-series	USA	Synthetic cannabinoids	• Auditory and visual hallucinations, paranoid delusions, odd or flat affect, thought blocking, disorganized speech, disorganized behavior, alogia, suicidal ideation, anxiety, distinct waxing and waning stoupourous appearance, insomnia, psychomotor retardation, psychomotor agitation
Faircloth et al., 2012 [61]	17-year old subject	Case-report	USA	Synthetic cannabinoids	• Confusion, inappropriate response to questions, combative behavior • Dizziness, lethargy, emesis, hyperventilation, hypertension, tachycardia, tachypnea, hyperglycemia, tremors, hypokalemia, fatigue, pallor, oxygen saturation 87% (room air)
Oluwabusi et al., 2012 [62]	2 adolescents (16–17 yy)	Case-report	Spain	Synthetic cannabinoids	• Low mood, insomnia, hyperactivity, anxiety, paranoid delusions, hallucinations
Young et al., 2012 [63]	A young adolescent (17 yy)	Case-report	USA	Synthetic cannabinoids	• Visual hallucinations • Lightheadedness particularly with standing, pounding in chest, chest pressure, chest pain, tachycardia followed by significant bradycardia, dyspnea on exertion
Thornton et al., 2012 [65]	A young adolescent (18 yy)	Case-report	USA	Synthetic cannabinoids and other substances	• Prolonged psychosis
Mensen et al., 2019 [64]	367 users (18–66 yy)	Questionnaire-based survey	Europe	Natural cannabis and synthetic cannabinoids	• Synthetic cannabinoid users were more likely to present with sleep problems, hypomanic symptoms, and higher scores of several dimensions of the Brief Symptom Inventory (BSI), including somatization, obsessive-compulsive behaviors, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. • Natural cannabis use was also highly prevalent in the synthetic cannabinoid user group, while synthetic cannabinoids use was non-prevalent in the natural cannabis user group.
Harris and Brown, 2013 [66]	6 adolescents and young adults (17–24 yy)	Case series	USA	Synthetic cannabinoids	• Agitation, hallucinations, and somnolence • Tachycardia, nausea/vomiting, chest pain syncope, seizure, inability to move arms, combativeness, hyper-reflexic

(*Continued*)

Table 1. (Continued).

Author(s), year of publication	Sample features	Type of study	Setting	Substances	Outcomes
Brewer and Collins, 2014 [67]	Case-studies	Review	Various	Synthetic cannabinoids	• Paranoia, hallucination, psychotic onset, anxiety, psychomotor agitation
Besli et al., 2015 [68]	16 pediatric patients	Retrospective cohort study	Turkey	Synthetic cannabinoids	• The most common physical symptoms were eye redness, nausea/vomiting, sweating, and altered mental status • The most common psychiatric symptoms were agitation, anxiety, hallucinations and perceptual changes
Roberto et al., 2016 [69]	1 adolescent (18 yy)	Case-report	USA	Synthetic cannabinoids	• Psychotic episode, insomnia, elated mood, agitation, paranoid ideation, thought insertion, thoughts broad-casting, bizarre delusional thoughts, disorganized behavior
Ninnemann et al., 2017 [70]	75 adolescents (12–19 yy)	Prospective cohort study	USA	Synthetic cannabinoids	• Depressive symptoms, but not anxiety or impulsivity, together with alcohol use and cannabis use predicted to synthetic cannabinoids' use
Gilley et al., 2018 [71]	75 adolescents (12–19 yy)	Observational study	USA	Synthetic cannabinoids	• 67% of adolescents developed neuropsychiatric symptoms
Tekulve et al., 2014 [73]	1328 adolescents (11–20 yy)	Retrospective cohort study	USA	Synthetic cathinones	• Fever, tachycardia, acidosis, development of seizure, hallucinations, and delusions
Khan et al., 2016 [72]	Two young adolescents (17 and 21 yy)	Case-series	USA	Synthetic cathinones	• Catatonia with/without psychotic onset

USA: United States of America; yy: years; N.A.: not applicable.

those of marijuana, these symptoms were at times more severe and unpredictable. Levels of psychomotor agitation, restlessness, anxiety, tachycardia, mildly elevated blood pressure, muscle fasciculation, and hypokalaemia described in a 17-year-old girl after having smoked SC [56]. With SC, psychotic symptoms, e.g. severe anxiety, paranoia and auditory/visual hallucinations, are frequently described [57]. Mood shifts have been described as well; a case-series reviewed the records of 11 US individuals aged 15–19 years who were evaluated after having smoked SC compounds. All reported feelings of euphoria and memory changes, whilst 9 out of 11 (82%) reported negative mood changes [58]. With the help of a semi-structured interview, a further study collected data regarding the use and effects of JWH-018, a synthetic cannabinoid, in 15 patients from early twenties to mid-forties (mean age 34) with serious mental illness in a New Zealand forensic and rehabilitation service [59]. After JWH-018 intake, subjects reported the onset of both anxiety and, in 69% of cases, psychotic symptoms [59]. A further case-series described 10 otherwise US healthy youngsters (range age: 21–25-years-old) admitted with new-onset psychosis to the psychiatric ward; auditory hallucinations (n = 4), visual hallucinations (n = 2), paranoid delusions (n = 9), odd or flat affect (n = 6), thought blocking (n = 4), disorganized speech (n = 6), disorganized behavior (n = 7), alogia (n = 3), psychomotor retardation (n = 6), psychomotor agitation (n = 3), and anxiety (n = 2) were all identified in these subjects [60]. After having smoked an SC compound, a 17-year-old male reported to feel dizzy and confused first, and then became combative [61]. Similarly, another paper described two cases of adolescents taking SC who developed a new-onset psychosis [62], both showing severe agitation, lability of mood, increased irritability, increased energy, insomnia, pressure of speech, disorganized behavior, flights of ideas, paranoid and grandiose delusions, auditory/visual hallucinations [63]. With the help of psychometric scales, a range of psychopathological symptoms associated with the use of SC and natural cannabis were compared in a sample of 367 European users; higher psychopathological suffering scores were identified with SC, including: sleep problems, hypomanic symptoms, and several dimensions the Brief Symptom Inventory (BSI), e.g. somatization, obsessive-compulsive behaviors, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism [64].

Many other case-studies reported similar findings [63–69]. Moreover, a longitudinal cohort study recruited adolescents (mean age: 16.09 years) from seven public schools in Texas. Depressive symptoms, marijuana use, alcohol use, and SC use at baseline were identified as predictive factors of SC use at 1-year follow-up, whereas anxiety symptoms and impulsivity were not [70]. An observational study described 75 adolescents (age range: 12–19-years-old) who had smoked SC; a range of neuropsychiatric symptoms was reported in 67% of them [71]. Finally, a paper described the occurrence of severe catatonia in two young adolescents who had self-administered with SC [72,73].

3.3. Use of synthetic cathinones; mental health issues and youngsters

A retrospective paper explored the American Association of Poison Control Centers (AAPCC) database to capture all known synthetic cathinone exposures amongst adolescents aged <20 years from January 2010 through January 2013 [73]. The authors reported a total of 1,328 synthetic cathinones' pediatric exposures; consistent with previous suggestions [74], 70.5% of these subjects were males, with an average age of 17 years. Psychiatric symptoms users exhibited by the users were psychomotor agitation and psychotic symptoms, such as hallucinations and delusions [75].

4. Discussion and conclusions

Although the association between NPS and mental health issues in young people is a particularly fascinating topic, it has not been yet well explored due to the limited information on NPS; the peculiar features of most NPS [1]; and the increasing levels of online exchange of NPS related-information [2]. Despite these limitations, to the best of our understanding we have been able to provide here the first, up-to-date, systematic, review of the use of NPS in youngsters and its association with mental health issues.

The ever-increasing number of NPS emerging worldwide and the parallel changes in drug scenarios represent a challenge for psychiatry, and especially so for child and adolescent psychiatry [1,4,8,12,14,21,34,36]. Vulnerable subjects, and indeed the technologically literate youngsters, may be exposed to a vast range of 'pro drug' web pages, which provide direct drug purchasing opportunities and/or drug information (e.g., description of the drug effects, dose, chemistry, and intake experiences) [13,14]. Advanced levels of knowledge relating to NPS are typically provided by drug fora/blog communities' members (e.g. the 'e-psychonauts' [1,13]). NPS favorable/unclear legal status in many countries has encouraged psychonauts and remaining drug users to supplement their habits with these new molecules [12–14].

Concerns about NPS impact on mental health arise from the observation that the intake of these substances is typically associated with changes of a range of neurotransmitter pathways/receptors whose imbalance has been associated with psychopathological conditions. Indeed, the occurrence of psychosis has been related (for a comprehensive review, see [1]) to: a) increased central dopamine levels, typically described with novel psychedelic phenethylamines, novel stimulants and synthetic cathinones; b) significant cannabinoid CB1 receptor activation, achieved with high potency synthetic cannabimimetics; c) 5-HT2A receptor activation, reported with latest generation phenethylamines, tryptamine derivatives, and hallucinogenic plants; d) antagonist activity at the N-methyl-D-aspartate (NMDA) receptors, described with ketamine, methoxetamine (MXE), and their latest derivatives; and e) k-opioid receptor activation, typically associated with Salvia divinorum ('Sally D') intake. One could also argue that, in comparison with adults, the central nervous system of children/adolescents may be more vulnerable to the activity of these molecules, hence raising even further the levels of mental health concerns [74–76].

Furthermore, the possibility of interactions among medical treatments and NPS should not be excluded and this may pose a risk in terms of efficacy of prescribed drugs; symptoms' worsening; and reduced adherence to therapeutic plans [76]. The NPS patterns of abuse; their multiple routes of administration; their wide range of potency; and the actual content of the NPS compound(s) ingested often pose a range of unanswered questions upon admission of youngsters to emergency rooms and mental health units [1]. Therefore, treatment decisions are often challenging, and prediction of associated potential risks and harms is often not known. In addition, due to the fast-moving nature of the NPS market, there is a limited availability of knowledge on the health implications and harms associated with the chronic use of NPS [1,10]. The inherently complex nature of NPS, with respect to their chemical heterogeneity, sustained emergence of new subcategories, and high prevalence and limited available clinical expertise, is contributing to significant public health threats [77]. Pharmacovigilance, and specifically proactive pharmacovigilance activities [76] which monitor and anticipate changes in drug abuse, using elements of clinical, epidemiologic, basic science, and social science expertise, are needed. Finally, contrasting the recently increasing expansion and availability of NPS, the successful example of some countries, where governments responded enacting legislation to reduce NPS trade and availability, resulting in a reduction in drug-related psychiatric admissions, should be considered [78,79]. Thus, in managing the increasing levels of diffusion of NPS, both prevention measures and legislation/drug control policies will need to be promoted and implemented worldwide.

5. Expert opinion

NPS constitute a challenging public health issue. Within the current drug scenario, where 'traditional' drugs of abuse are both controlled and easily identified, NPS may be seen as attractive, and especially so for young people. This is particularly true for synthetic cannabinoids whose external appearance looks similar to the vastly popular organic cannabis preparations. However, in comparison with marijuana/hashish, synthetic cannabinoids are: undetectable in standard toxicology tests; significantly more powerful, since lacking any cannabidiol concentration, which may powerfully modulate the dopaminergic THC effects [1]; largely available from the web; and affordable [1,7]. The evidence here presented, referring to both the European and worldwide NPS scenarios [3,4,8], emphasizes the significant use of synthetic cannabinoids and central nervous system stimulants, such as mephedrone/remaining synthetic cathinones, among NPS abusers. Overall, however, poly-substance abuse is likely to be the norm in the NPS scenario [4,34–37,39,40,42,51,73].

Current results may suggest that high levels of NPS use may be identified in people diagnosed with psychotic; personality; or bipolar disorders [36,41,54,55,62,69]. Hence, the comorbidity of NPS use with psychopathological issues should be considered as a public health issue. NPS use, per se, may trigger de novo psychopathological issues but can worsen as well already existing mental health conditions [1,52,53,55–68,70–72]. One limitation of the studies here identified and described, however, is that a clear-cut differentiation between mental illness and psychiatric symptoms that can be evoked by NPS use needs to occur. For example, many case series and case reports here included mentioned indeed psychiatric symptoms (e.g. anxiety) following NPS/SC use, but no formal mental health disorders. In other words, one could argue that the use of NPS can, in most cases, evoke psychiatric symptoms, but not necessarily mental health disorders.

Planning/implementing a range of prevention activities through information and education, aiming at decreasing youngsters' levels of access to NPS, should be considered. NPS intake and mental health issues should be better investigated in longitudinal studies, since virtually nothing is known about the long-term consequences of NPS use on the mental and physical health of vulnerable people. Furthermore, more studies specifically focused on youngsters (<20-years old) should be performed, in order to evaluate the exact correlation between the ingestion of each specific NPS and the associated mental health issues. More precisely, we need to better understand and describe in detail the role of increased vulnerability for subjects with and without a history of mental disorders. In addition, future longitudinal, large sample size, studies should consider the use of clinical/psychopathological data at baseline and their possible modification overtime in association with NPS intake whilst eliminating potential confounding factors. Finally, the neuroimaging correlates of the NPS intake effects on an adolescent subject, who is per definition in his/her growing phase of cerebral maturation, needs to be better understood.

Clinicians should improve their awareness of drug safety issues, aiming at being better educated in recognizing NPS-related toxicity issues, so that potentially life-threatening complications can be treated and managed properly. Drug control policies should be improved, and the list of NPS should be constantly updated with improvement in detection methods. Given the implication on mental health, psychiatric services should adapt to the new drug scenarios, developing innovative engagement strategies, and building new therapeutic pathways that may improve service integration levels [60].

In parallel with constant changes in basic scaffolds from which novel molecules can be derived/designed/synthesized, the NPS market will continue to grow. It is likely that increasing levels of interest will be given in the near future to the misuse of both prescribing compounds and 'herbal highs'. Overall, this will pose a challenge, since NPS-related toxidromes are, per se, complex and unpredictable. Long-term studies, analyzing NPS-related consequences, and specifically in young subjects, will be encouraged. Consistent and updated drug monitoring practices will be improved. A proactive pharmacovigilance approach will monitor and anticipate changes in future drug abuse scenario. A combination of prevention activities and control policies will hopefully better deter vulnerable populations from accessing NPS compounds.

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