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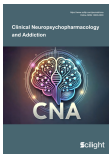

Review

Psychopathology and Psychiatric Risks Linked to High-Potency Cannabis, Crack Cocaine and Novel Psychoactive Substances

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Abstract: Background: High potency cannabis (HPC), crack cocaine, and novel psychoactive substances (NPS) have significantly reshaped the landscape of substance-related psychopathology. This transformation is driven both by the increased psychoactive potency of known substances and by the emergence of new synthetic compounds. The aim of this paper is to provide a practical clinical reference for settings lacking laboratory support. **Methods**: This study analyzes 69 articles published between 2015 and 2025, encompassing a total of 126,365 patients reporting symptoms associated with the use of HPC, crack, and NPS. **Results**: HPC is associated with an increased risk of acute and persistent psychosis, seems proportional link to THC concentration. Synthetic cannabinoids are also frequently associated with acute psychosis, hallucinations, and delusions. Cathinones are associated with psychotic symptomatology, while crack cocaine is primarily linked to mood disorders, depressive symptomatology, and suicidality. **Discussion**: Increasing THC concentrations in HPC appear to be associated with more severe psychotic manifestations, such as paranoia, aggression, and hallucinations. Synthetic cannabinoids can trigger auditory and visual hallucinations, underlining that stimulation of the endocannabinoid system can elicit pronounced psychotic symptomatology. Cathinones are also associated with psychotic symptomatology, with a more heterogeneous presentation, but can additionally induce alterations of vital parameters and elevated Creatine Phosphokinase (CPK) levels. Depressive symptomatology is predominant in crack cocaine use, while all substances under review demonstrate an association with anxiety symptoms. **Conclusions**: All three substance groups constitute a major and evolving challenge for mental health services. Distinctive symptom profiles can guide identification and evidence-based management in resource-limited settings.

Keywords: high-potency cannabis; crack cocaine; novel psychoactive substances (NPS); psychopathology; psychosis; depression

1. Introduction

Substance Use Disorder (SUD) is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5-TR) as a clinical condition characterized by a persistent and maladaptive pattern of psychoactive substance use, associated with significant impairment in personal, interpersonal, and social functioning [1]. In the

DSM-5-TR, the classification system for substance-related disorders underwent substantial revision compared to previous editions. Specifically, the conceptual and diagnostic dichotomy between substance abuse and substance dependence was eliminated, as these categories had proven inadequate in clinical practice to capture the continuum and phenomenological complexity of pathological substance use. To address this, the DSM-5-TR introduced the new unified diagnostic category of SUD—framed within a dimensional perspective that allows for assessment of the disorder's severity based on the number and pervasiveness of clinical criteria met. This reformulation provides a diagnostic framework that more accurately reflects clinical reality, in which loss of control over substance intake, persistence of use despite adverse consequences, craving, and neurobehavioural adaptation (tolerance and withdrawal) are considered central features. The DSM-5-TR further specifies ten primary classes of substances capable of inducing this disorder, including: alcohol, cannabis, opioids, stimulants, hallucinogens, as well as substances less commonly addressed in clinical contexts, such as caffeine and inhalants [1]. This broad categorization reflects growing awareness of the potentially deleterious neuropsychiatric impact of a wide range of psychoactive agents, both licit and illicit. SUD thus represents one of the major challenges in contemporary psychiatry, due both to its increasing prevalence and to its complex presentation, often involving psychiatric symptoms, particularly of a psychotic nature [2].

Against a background of recent clinical and epidemiological changes, the phenomenology of SUD has undergone profound transformations, attributable both to the increased psychoactive potency of many established substances and to the emergence of new synthetic compounds—Novel Psychoactive Substances (NPS), with onset of substance use increasingly occurring during adolescence. In 2023, cannabis use was estimated to involve approximately 14 million students aged 15–16 years worldwide [3]. In the United States, between 2018 and 2020, the prevalence of daily cannabis consumption increased by roughly 1% across multiple compulsory school age groups [3]. In recent years, the use of high-potency cannabis (HPC), defined by a THC content greater than 15%, as increased significantly, including in Europe. The potency of herbal cannabis (marijuana) increased in the period 2010–2019 from an average THC concentration of 6.9% to 10.6%, while the median THC concentration in cannabis resin (hashish) tripled, rising from 7.6% to 24.1% [4]. These increases in THC content, often without the moderating effects of cannabidiol (CBD), represent a key clinical concern. The use of more potent cannabis products is associated with an increased risk of mental disorders—particularly psychotic disorders—and has contributed to a rise in treatment admissions for cannabis-related problems [4]. Methods of HPC administration include both traditional approaches—such as smoking (handmade cigarettes like joints, pipes, or bongs) or ingested in the form of edible compounds—and more modern devices like vapourizers and extracted concentrates (e.g., butane hash oil, wax, budder), which may contain THC levels exceeding 60% [3]. HPC produces significantly more intense pharmacological effects compared to low-THC strains due to its increased partial agonism at the cannabinoid CB1 receptor, which is abundantly expressed in the limbic system, prefrontal cortex, and basal ganglia [5]. Prolonged interaction with these receptors modulates the release of key neurotransmitters—including dopamine, gamma-aminobutyric acid (GABA), and glutamate—thereby altering neurotransmission and neuroplasticity. Indeed, increased glutamate concentrations in regions such as the striatum and anterior cingulate cortex potentially contribute to excitotoxicity and neural dysregulation [6]. Functional neuroimaging studies have also demonstrated THC-induced dysfunction within cortico-subcortical circuits, further supporting its potential neurobiological contribution to the development of psychotic disorders. In genetically predisposed individuals, exposure to HPC has been associated with a dose-dependent increase in the risk of developing affective psychosis and schizophrenia-spectrum syndromes, with an odds ratio greater than 4 among daily HPC users compared with non-users [7].

Among currently most used psychoactive substances, crack cocaine holds particular clinical relevance due to its high-potency. Crack cocaine is a smokable form of cocaine obtained through a cooking process that transforms the substance into solid crystals. Inhalation of the vapours produced by combusting these crystals enables extremely rapid absorption through the alveolar epithelium, resulting in an almost immediate onset of psychoactive effects. Epidemiological data on cocaine use often fail to distinguish between powdered cocaine and crack cocaine, making it difficult to accurately estimate the true prevalence of crack consumption. Nevertheless, according to the World Drug Report (2023), the market of substances was marked by a globally increased use of cocaine [8]. Symptoms including intense craving, impulsive behaviours, and transient psychotic symptoms, often compounded by severely disadvantaged social contexts, are associated to the use crack cocaine. Consumption typically occurs through pipes or improvised devices and is characteristically linked to compulsive patterns of use and binge episodes [9]. The use of crack cocaine, which acts as a potent inhibitor of monoamine reuptake—particularly dopamine—by blocking the dopamine transporter (DAT) in the nucleus accumbens [10], has been associated with severe psychiatric symptoms [11]. This dopaminergic surge induces an intense but short-lived euphoric state, followed by compulsive craving and dysphoria. Repeated use leads to dopaminergic and

glutamatergic neuroadaptations that reinforce the craving–reward cycle and promote the development of dependence. From a psychiatric standpoint, crack cocaine use is frequently associated with paranoid psychotic episodes, marked impulsivity, and the exacerbation of pre-existing psychiatric comorbidities [12].

NPS constitute a broad and heterogeneous group of compounds encompassing multiple chemical and effect categories. The most prevalent classes include synthetic cannabinoids and synthetic cathinones, followed by dissociatives, psychedelics, hallucinogens, synthetic opioids, and others. A defining feature of many of these substances is the presence of "novel" molecular structures deliberately engineered to circumvent existing legal controls. Between 2010 and 2023, the number of NPS identified on the market increased substantially, reaching peaks of up to 600 new compounds identified in a single year [8]. Among the various classes, synthetic stimulants and synthetic cannabinoids consistently remain the most commonly represented. NPS, often marketed through the Internet and social media under misleading names and without regulatory traceability, are particularly appealing to younger populations [13]. NPS are difficult to detect through standard toxicological screenings and are associated with increasing clinical exposure despite limited understanding of their long-term effects [14]. Certain classes of NPS—particularly synthetic cannabinoids, cathinones, and novel opioids—show a significant association with suicidal and self-injurious behaviours [14], presenting new and complex challenges for early diagnosis, prevention, and therapeutic intervention in psychiatric settings. The use of NPS is progressively expanding, particularly among vulnerable populations such as young adults, incarcerated individuals, and habitual users of psychoactive substances. The vast heterogeneity of NPS exposes users to a high risk of adverse events, especially due to their inability to predict and appropriately manage the effects of the substances consumed [15]. This compromises self-regulation of use and increases the likelihood of abuse.

It is also important to note that current toxicological screening methods are limited by outdated or insufficiently comprehensive panels and by the rapid evolution of the drug market. This represents a significant obstacle to timely clinical management, reducing the effectiveness of emergency interventions and complicating the implementation of safe treatment protocols [15]. The main classes of currently widespread NPS include synthetic cannabinoids (e.g., JWH-398), cathinones such as mephedrone, designer benzos, novel synthetic opioids (e.g., nitazenes), phenethylamines and their derivatives, including NBOMe compounds (a molecular class characterized by the *N*-2-methoxybenzyl group). Routes of administration for NPS are heterogeneous and depend on their pharmacological class; these substances may be inhaled, taken orally, injected, or smoked [16,17].

Within this heterogeneous group of synthetic compounds, many exhibit high potency and rapid onset of action. For example, synthetic cannabinoids act as full agonists at CB1 receptors, with substantially greater efficacy than THC, resulting in amplified side effects such as severe anxiety, psychomotor agitation, paranoid delusions, and acute psychotic episodes [18]. Stimulant NPS, structurally and pharmacologically similar to amphetamines, markedly increase the release of dopamine and norepinephrine, promoting manic states, impulsive behaviours, and persecutory delusions [19,20]. Chronic use of NPS has been associated with cognitive deterioration, affective dysregulation, and persistent psychosis, often resistant to conventional antipsychotic treatment [21].

The pharmacodynamic and pharmacokinetic profiles of the above-mentioned substances contribute to considerable complexity in acute-phase therapeutic management and represent a growing clinical challenge in emergency settings. Treatment assessment and differential diagnosis are particularly complicated by the fact that symptom presentation often overlaps with that of primary psychotic disorders, including the acute onset of persecutory delusions, auditory hallucinations, thought disorganization, and psychomotor agitation. Moreover, the substantial chemical and pharmacological variability of these substances can make their identification difficult—if not impossible—in urgent care contexts, delaying the establishment of targeted treatment protocols and increasing the risk of rehospitalization and chronicity of psychiatric symptoms. Added to this, the neurovegetative and behavioural instability frequently observed, particularly in cases related to NPS and crack use, necessitates prompt and tailored intervention involving pharmacological containment, intensive monitoring, and integrated clinical support [22].

Recent epidemiological data show steadily increasing in illicit substance market, raising concern due both to the high prevalence of use among young people and to the severity of associated adverse effects. To the best of our knowledge, there is a paucity of literature providing comprehensive syntheses to guide clinicians in differentiating psychopathological manifestations. This review, therefore, aims to offer a practical resource to support diagnostic assessment and clinical management. Given that these substances frequently present with anxiety, depression, and psychosis, our analysis focuses primarily on these domains.

2. Materials and Methods

To select the articles for this narrative review, we conducted a literature search in English on 1 April 2025, using a combination of controlled vocabulary and keywords: ("high potency cannabis" OR "skunk" OR "crack" OR "NPS" OR "cathinone" OR "spice") AND ("psychosis" OR "depression" OR "mood disorder" OR "anxiety") NOT (review OR mouse OR animal). The search was restricted to articles published in the past 10 years and was conducted in the PubMed and Scopus databases.

3. Results

This yielded 764 records from PubMed and 1801 from Scopus. After excluding non-original articles, non-English publications, and studies not specifically addressing psychiatric symptoms related to HPC, crack or NPS, a total of 69 articles were included in the final analysis. The results are organized by substance to facilitate thematic analysis. A summary of the most relevant data extracted from these studies is provided in Table 1.

3.1. High-Potency Cannabis

The risk of developing psychosis appeared to be closely linked to THC concentration. The use of cannabis containing more than 10% THC was associated with a substantially higher and more prolonged risk of psychosis, persisting significantly longer even after cessation of use, compared with cannabis containing less than 10% THC [23]. Other studies examined the acute effects of cannabis with varying concentrations of THC and CBD. Findings indicate that cannabis with high concentrations of CBD (>70%) produces significant anxiolytic and relaxing effects [24], whereas high concentrations of THC are associated with acute psychotic symptoms, including paranoia and aggression [24,25].

In recent years, the pro-psychotic effects of HPC were demonstrated by an increasing body of evidence.

A large-scale study—conducted in the state of Colorado between 2013 and 2018, encompassing all emergency departments statewide—reported a significant rise of psychotic episodes following the legalization of cannabis in the state of Colorado [26]. Furthermore, an increase in anxiety- and depression-related complaints was also observed [26]. Conversely, several studies reported no significant impact of HPC on anxiety and depressive symptoms, while concurrently highlighting its causal role in increasing the risk of developing psychosis [27–29].

The correlation between THC concentration and psychotic symptoms was strongly documented among adolescents who use cannabis (mean age 16.8 years). Exclusive use of HPC, such as "skunk", doubled the risk of developing paranoia, as well as anxiety and insomnia. Moreover, higher quantities of use are associated with an increased risk of more severe psychotic symptoms, such as hallucinations [30]. Several case reports described individuals who, after consuming butane hash oil with THC concentrations exceeding 80%, developed acute psychosis characterized by prominent paranoid delusions, hallucinations, and disorganized behaviour. These symptoms typically resolved only after cessation of cannabis use and treatment with second-generation antipsychotics [31,32]. Patients diagnosed with schizophrenia spectrum disorders tend to prefer using HPC over strains with high CBD content, perceiving the latter as 'not strong enough' [33]. A study on selonabant, a CB1 receptor antagonist, demonstrated its efficacy in blocking psychotic symptoms induced by HPC, further underscoring the direct role of THC in the onset of such symptomatology [34]. However, some studies based on moderately large samples reported that the use of HPC was not associated with an increased risk of developing psychotic symptoms or aggression, but rather with a higher likelihood of dependence [35–37].

3.2. Crack Cocaine

Borderline Personality Disorder, Generalized Anxiety Disorder (GAD), mood disorders, and suicidal behaviours were among the most frequently comorbidities reported as associated with crack use [38]. GAD, and more broadly moderate to severe anxiety symptoms, were commonly observed in individuals who actively use crack [39–41]. The presence of such symptoms significantly increased the likelihood of crack use compared with individuals presenting with mild or no anxiety symptoms [39]. Indeed, several studies reported prevalence of anxiety symptoms among crack-dependent individuals (70% to 80%) [40,41]. Nevertheless, the most common comorbidity among regular crack users appeared to be depressive disorders. Nearly all recent studies on crack addiction reported the presence of depressive symptoms [38,40–46]. Interestingly, some investigations focused specifically on the dimension of hopelessness, highlighting that crack users are often characterized by profoundly adverse socioeconomic conditions and life styles [41]. This becomes particularly relevant when considered alongside research demonstrating a strong association between crack use, depressive symptoms, and suicidal

ideation or behaviours [38,44,45]. Among depressive symptoms, hopelessness and loneliness are identified as key predictors of suicidal acts.

3.3. Novel Psychoactive Substances

Within the broad category of NPS, certain groups of compounds were more prominently represented than others, both in terms of consumption patterns and, consequently, in the volumes of scientific literature dedicated to them. Synthetic cathinones and synthetic cannabinoids constituted the two most extensively studied and widely consumed subgroups. Cases involving other categories of NPS are seldom reported in the literature—for example, ketamine derivatives such as methoxetamine. The latter substances can induce clinical presentations marked by pronounced dissociative symptoms and affective blunting [47]. The category of synthetic cathinones included several hundred compounds, among which mephedrone and 3,4-methylenedioxypyrovalerone (MDPV) are the most representative substances. Mephedrone was associated with a high incidence of anxiety and paranoid psychotic symptoms, highlighting its significant neuropsychiatric impact [48–51]. Specifically, compared with the use of other psychostimulant substances such as 3,4-methylenedioxymethamphetamine (MDMA), the incidence of psychiatric symptoms was significantly higher among mephedrone users, and, more notably, such symptoms tend to persist considerably longer [48].

In addition to anxiety-related symptoms, psychotic symptomatology is commonly reported, characterized by paranoid delusions and predominantly visual hallucinations, often accompanied by aggressive behaviours triggered by compulsive consumption [49,50]. One case report described the emergence of psychotic symptoms, including grandiose delusions and multisensory hallucinations, following the use of mephedrone and α-PVP. In such instances, the psychotic symptomatology may persist for several months [52]. Similarly, MDPV use is also associated with the onset of psychotic symptoms, including delusions, hallucinations, and frequently psychomotor agitation [53]. MDPV is often consumed in the context of polydrug use, particularly with other synthetic cathinones such as α-PVP, which can exacerbate acute psychotic symptoms accompanied by severe agitation [54]. This type of psychotic symptomatology is generally characterized by paranoid themes [55]. In cases of polysubstance abuse involving the simultaneous use of multiple synthetic cathinones, agitation is more frequently reported in addition to psychotic symptoms [54,56].

In specific categories of patients, such as patients undergoing opioid substitution therapy who concurrently used MDPV or other synthetic cathinones, a worsening of psychiatric symptoms was observed in all reported cases, particularly regarding depressive symptomatology [57,58]. Another synthetic cathinone deserving attention is *N*-ethylpentylone (ephylone). This compound was identified in patients who reported concomitant use of other stimulant substances such as MDMA and mephedrone. Nearly all patients presenting for medical evaluation exhibited psychomotor agitation, aggressive behaviour, and sympathomimetic hyperactivation with elevated CPK levels, whereas only a subset displayed psychotic symptomatology characterized by paranoia and hallucinations [59,60]. Several cases reported the acute onset of psychotic symptoms following the use of unidentified synthetic cathinones. These substances were sometimes found in sweetened gummy candies or instant coffee sachets, or more commonly marketed as “bath salts.” In those cases, psychotic presentations were characterized by a broad symptom spectrum, ranging from isolated paranoid delusions to visual hallucinations accompanied by aggressive behaviours [61–63]. The clinical presentation almost always included hallucinations, paranoid-themed delusions, and, in several cases, sympathetic nervous system hyperactivation [64–66]. Comparative studies between synthetic cathinones and methamphetamine emonstrated largely overlapping psychiatric symptomatology, although synthetic cathinones much more frequently provoke severe sympathomimetic hyperactivation [67,68]. The use of long half-life synthetic cathinones, such as α-pyrrolidinohexanophenone (α-PHP) was characterized by frank psychotic symptoms, including delusions, hallucinations, and aggressive behaviour [69], with an extremely variable duration of symptoms, which in some cases progressed to persistent psychosis [70–72].

A second major group of NPS recorded included synthetic cannabinoids. Synthetic cannabinoids were reported with a 30-fold increased risk of requiring emergency medical treatment compared with natural cannabis, being most common reasons for medical evaluation including anxiety, paranoid ideation and agitation, observed in approximately half of the cases [73–76]. Multiple case reports describe acute psychotic states characterized by symptoms such as paranoid delusions, visual and auditory hallucinations, psychomotor agitation, and aggressive behaviour [77,78]. Patients dependent on 5F-AKB48 and 5F-PB-22, two synthetic cannabinoids, have developed acute psychopathological episodes during withdrawal. Reported symptoms included anxiety, depression, and paranoid states [79,80].

Comparing regular users of synthetic cannabinoids with healthy controls, users exhibited significant executive function impairments [81]. A comparative study of patients with schizophrenia and those with synthetic

cannabinoid–induced psychosis demonstrated that the latter displayed a less pronounced burden of negative symptoms, while presenting a comparable profile of positive symptomatology and a notable prevalence of suicidal ideation [82].

Atypical symptoms induced by synthetic cannabinoids were also documented. One case involved an 18-year-old male who developed a manic episode following the use of large quantities of synthetic cannabinoids [83]. Another case described the occurrence of severe rhabdomyolysis in the context of an acute psychosis characterized by paranoid delusions and intense psychomotor agitation [84]. Finally, an 18-year-old individual developed Hallucinogen Persisting Perception Disorder (HPPD) following the use of a synthetic cannabinoid known as JWH-122. The clinical picture included anxiety states and depersonalization, with symptoms persisting for approximately four years before eventually resolving [85].

3.4. Mood-Related Effects

During this review, data concerning mood-related effects emerged incidentally. As these did not represent the primary focus of this investigation, they are presented as secondary results. Indeed, HPC, particularly when containing a THC concentration > 84.99%, produced euphoric effects, although without evidence of full-blown manic symptomatology [24]. Mood dysregulation was described as resulting from crack use, characterized by disinhibition and affective instability [38]. While neither manic or dysphoric symptoms have been reported with cathinones, synthetic cannabinoids appears to be the only substance examined that has been associated, albeit rarely, with overt manic symptomatology [83]. In the latter instance, the reported symptomatology is underpinned by key neurobiological mechanisms. Specifically, the high concentrations of THC present in HPC induce psychotic symptoms—such as paranoia, aggression, and hallucinations—through the agonist action of THC on the endocannabinoid system (primarily CB1 and CB2 receptors), subsequently eliciting dose-dependent dopamine release within the mesolimbic pathway [86,87].

Crack cocaine exerts its effects by binding to monoamine transporters and inhibiting their reuptake, thereby raising extracellular monoamine levels across multiple brain regions. In particular, it produces a pronounced elevation of dopamine within the ventral striatum and nucleus accumbens, eliciting intense euphoria and positive reinforcement that translate into marked craving. This mechanism likely contributes to the high prevalence of crack use among individuals with pre-existing mood disorders [10].

NPS primarily encompass stimulants such as cathinones and synthetic cannabinoids. Despite their wide-ranging pharmacokinetic profiles, these substances often share a marked psychotoxic potential, frequently inducing acute psychotic episodes characterized by aggression, disorganization, and, in some cases, autonomic disturbances. Certain synthetic cathinones, such as mephedrone, act on monoamine transporters as releasing agents, promoting the efflux of neurotransmitters into the synaptic cleft [88]. Others, such as MDPV and α-PVP, act as monoamine transporter blockers, inhibiting neurotransmitter reuptake [89]. This massive monoaminergic activation partially accounts for the emergence of positive psychotic symptoms and sympathomimetic hyperactivation. Synthetic cannabinoids act as high-affinity full agonists at CB1 and CB2 receptors. This strong activation of the cannabinoid system produces pronounced dopaminergic disinhibition within mesolimbic circuits, and the resulting massive dopamine release is believed to underlie their psychotogenic effects [90,91].

Table 1. Summary of the main psychopathological aspects associated with the substance classes examined.

Substance		Number of Patients	Anxiety Symptomatology	Depressive Symptomatology	Psychosis		
					Psychotic Behaviour	Delusion	Hallucination
	HPC	M/49858 F/31990	Anxiety symptoms have been associated with the use of high-THC cannabis [24]. However, observational studies in large population samples do not show an increased incidence of anxiety associated with cannabis use [26].	No clear correlation with depressive symptoms has been reported in relation of HPC.	The use of high-THC cannabis products (skunk, BHO, dab) is consistently associated with psychotic-like behaviours, including cognitive disorganization, social withdrawal, agitation, and aggression [31,32].	Concentrates such as BHO, dab, and skunk have been associated with acute paranoid delusions, persecutory ideation [31,32].	Hallucinations, particularly auditory, have been more frequently reported among users of skunk, BHO, or THC-dominant chemovars (THC > 15%, CBD < 1%), especially when consumption reaches or exceeds two joints per episode [30,31].
	Crack	M/3095 F/1834	Anxiety has been reported recurrently among crack users. Many individuals develop a true generalized anxiety disorder [38,39].	Depressive symptoms have been frequently reported (up to 72%), often severe, and commonly co-occurring with hopelessness and suicidal ideation [40,41,45].	No cases of psychotic behaviour have been reported	No cases of delusion have been reported	Hallucinations have been reported as a significant psychopathological symptom. They were found to be significantly associated with suicide attempts [44].
NPS	Synthetic cathinones	M/2030 F/744	Anxiety symptoms have been frequently reported. Mephedrone is linked to higher anxiety and longer recovery. Severe anxiety is common in cathinone intoxications. Alpha-PHP is linked with anxiety [48,57,70].	Depressive symptoms have been rarely reported but, in some cases, suicidal ideation was mentioned [51,57].	Psychotic behaviour has been frequently reported. In particular: agitation disorganization and aggression are often correlated with high concentrations of MDPV and α-PVT [52,70].	Delusions have been documented as paranoid ideation, in MDPV and other cathinones consumption. also, persecutory and grandiose delusions have been reported [52,55,64].	Hallucinations have been commonly reported. They are primarily related to the use of different type of cathinones and can be multisensory, visual or coenesthetic [49,51,59].
	Synthetic cannabinoids	M/22.933 F/13881	Anxiety symptom have been frequently associated with synthetic cannabinoid use, occurring both during acute intoxication (panic attacks, agitation) and during withdrawal [73,79,80].	Depressive symptoms have been reported in several studies, both during acute use and withdrawal. Suicidal ideation, and suicide attempts were observed, particularly among adolescents and heavily dependent users, indicating a significant affective risk [74,79,80].	Psychotic behaviour has been reported; iIn particular: characterized by rapid onset presentation and aggressiveness [78,84].	Delusions, primarily of a persecutory nature, have been observed in acute psychotic states induced by synthetic cannabinoids [73,76,80,84].	Hallucinations, both visual and auditory, are frequently reported during acute intoxication [77,78] A case of Hallucinogen Persisting Perception Disorder has also been reported [85].

Abbreviations: HPC: high-potency cannabis, THC: tetrahydrocannabinol, NPS: Novel Psychoactive Substances; MDPV: 3,4-methylenedioxypyrovalerone.

4. Discussion

The findings of this review highlight the psychiatric complications associated—through varying degrees of causal relationships—with the use of HPC, crack cocaine, and NPS. These substances represent three of the most prevalent classes of drugs abused in the current era and are characterized by distinct symptom profiles. HPC is strongly associated with acute psychotic symptoms, particularly in adolescent populations, with a dose–response relationship between the duration of use and the risk of developing psychosis. Notably, more severe psychotic manifestations—such as paranoia, aggression, and hallucinations—were observed with increasing concentrations of THC. Synthetic cannabinoids were similarly characterized by psychotic symptoms, most notably persecutory delusions, hallucinations, and aggressive behaviour, often with explosive manifestations. In particular, hallucinations induced by synthetic cannabinoids were both auditory and visual, whereas in HPC users only auditory hallucinations were described. This further supports the notion that stimulation of the endocannabinoid system can elicit pronounced psychotic symptomatology [90].

Synthetic cathinones were also associated with psychotic symptomatology, although with a more heterogeneous presentation, including not only persecutory delusions but also grandiose themes. Hallucinations likewise appeared heterogeneous, as they may be visual, coenesthetic, and multisensory, and only rarely limited to the auditory modality. In some reported cases, cathinones induced clinical presentations characterized by elevated CPK levels and significant alterations in vital parameters.

This phenomenon was also described in association with other NPS, such as phencyclidine (PCP), a dissociative formerly used as an anesthetic and, in recent years, increasingly misused as a recreational drug. PCP use has been linked to physical symptoms including tachycardia, hypertension, nausea, vomiting, and renal failure [92]. Among the articles analyzed, in relation to crack abuse, only hallucinations are reported as a psychotic manifestation. Crack abuse is instead primarily associated with prominent depressive symptomatology, particularly characterized by feelings of hopelessness and suicidal behaviours. This should prompt clinicians managing psychiatric patients who abuse crack cocaine to pay particular attention to these aspects.

Depressive symptomatology were not reported in association to HPC, whereas in the case of NPS it is occasionally present. Synthetic cathinones were associated with depressive symptoms, albeit in a minority of cases. The use of synthetic cannabinoids is more frequently linked to depressive symptomatology, documented both in cases of acute intoxication and during withdrawal. In both these NPS classes, depressive symptoms are often accompanied by self-harming ideation or behaviours, which may provide further evidence of the marked potency that frequently characterizes NPS.

All substances here reported demonstrated an association with anxiety symptoms, which appear to be virtually ubiquitous.

These findings underscore how psychiatric symptoms are increasingly intertwined with the use of psychoactive substances. The results presented here are broadly consistent with those of other recently published studies. Several recent systematic reviews have examined the effects of HPC consumption, highlighting that adverse outcomes are directly proportional to THC concentrations [93–95]. At the same time, a particularly strong association between HPC use and psychotic disorders emerged, in contrast to anxiety and depressive symptomatology, although these were also present. This pattern is, therefore, consistent with our findings [94–96].

The recent literature remains limited with respect to articles specifically addressing crack use, probably due to the difficulty of identifying exclusive crack users in scientific studies. Nevertheless, recent reviews highlighted that crack consumption is clearly associated with all psychopathological dimensions, particularly affective dysregulation and psychotic symptomatology [96,97].

Available studies on NPS primarily focused on the different subcategories of this drug class. Specifically, in the case of HPC, several studies emphasized the greater severity and persistence of psychotic disorders induced by its use compared with natural cannabis [96–98]. Recent literature also shown particular interest in synthetic cathinones. Several reviews report high rates of psychotic symptomatology, often accompanied by violent and aggressive behaviours as well as neurological manifestation [19,98,99].

In some cases, substance use exacerbates pre-existing psychiatric conditions; in others, it induces new symptomatology in individuals with no prior psychiatric history, often presenting with abrupt and severe manifestations. It is, therefore, essential to accurately differentiate substance-induced symptoms from primary psychiatric disorders in order to effectively identify and manage the evolving trajectories of contemporary psychopathology. This is particularly relevant in chronic psychiatric conditions complicated by substance dependence—as is commonly observed with crack cocaine and HPC—as well as in acute psychiatric episodes presenting in emergency settings, which are frequently linked to NPS use. The latter poses a unique clinical challenge due to the difficulty of detecting these substances with standard laboratory screening, a consequence of

their chemical variability. Moreover, improved knowledge of these substances and their psychiatric implications may facilitate the early identification of at-risk individuals, such as young users of HPC or mephedrone.

This review has several limitations. As this is a narrative review, it inherently lacks a systematic search strategy encompassing multiple databases and 'grey literature', and likewise it does not employ a reproducible methodology. Moreover, the studies examined are highly heterogeneous in terms of methodology, study populations, and diagnostic instruments used, all of which may represent potential confounding factors. However, the narrative nature of the review allows greater accessibility to readers who may not possess a solid background in the field of addiction, by collecting and comparing the psychopathological characteristics of three groups of substances that are currently among the most widely used on the market. In this sense, this work may serve as a useful tool for clinicians, who are increasingly required to identify and manage psychopathological phenomena associated with these substances of abuse.

5. Conclusions

In conclusion, the use of HPC, NPS, and crack currently constitutes a major challenge to mental health. Each substance is associated with distinct patterns of use and characteristic symptomatology, requiring evidence-based prevention, diagnostic, and treatment strategies tailored to their unique profiles. This underscores the need for clinicians to recognize the involvement of these substances on the basis of their clinical presentation. The present article seeks to furnish clinicians with a practical tool for accurately identifying such cases, especially in settings where laboratory support is unavailable.

Further research is needed to enhance our understanding and ability to disentangle the causal relationships between psychiatric disorders and substance use, as well as to deepen knowledge of a rapidly evolving landscape. A more accurate characterization of the clinical presentation of each class could be achieved by conducting additional investigations focusing on single compounds. Moreover, improved comprehension of these substances should inform the development of more effective public education strategies aimed at preventing potentially harmful patterns of use.

Author Contributions

T.P.: writing—original draft preparation and editing A.S.: data curation, visualization, writing; F.M.: data curation, visualization, writing; A.R.: data curation, visualization, writing; A.M.: methodology; G.M.: conceptualization, supervision. J.M.C.: reviewing, writing, language consultant. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries should be directed to the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest. Given the role as the Editor-in-Chief, Giovanni Martinotti had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

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