LETTER TO THE EDITOR

New psychoactive substances and altered consciousness: An emerging challenge for public health

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To the editor,

Delayed awakening from coma remains an unresolved clinical challenge. A recent study reported a point prevalence of coma ranging from 7 to 31 per 100,000 and an annual incidence between 135 and 258 per 100,000 individuals (1). The causes of impaired emergence are often multifactorial. Clinicians routinely consider a broad spectrum of etiologies, including prolonged sedation, electrolyte imbalances, and cerebral edema. However, one emerging factor remains insufficiently explored. There appears to be a "grey zone" in which coma emergence is delayed without a clear cause, and when awakening does occur, it is frequently complicated by significant alterations in consciousness. The use of recreational drugs is widespread, particularly among young people, who are often involved in polytrauma while under the influence of substances that impair sensory and reactive capacities. Among the wide array of psychoactive agents, the so-called New Psychoactive Substances (NPS) are increasingly prevalent. The most common NPS include synthetic cannabinoids (for example AB-CHMINACA, AB-FUBINACA, JWH-171, JWH-176) cathinones (for example methylenedioxypyrovalerone (MDPV), methylone or mephedrone and pyrovalerone, novel benzodiazepines (for example rilmazolam, diclazafone deglycinate; clonazafone deglycinate; noravizafone deglycinate), and phenethylamines (for example 25I-NBOMe, la 2C-B, la 2C-H, la 2C-E, la DOB, la DOC, la 4-FA, la 4-MA, la PMA e la PMMA). The toxicodynamics of these compounds are not yet fully understood. The effects on the central nervous system involve both the excitatory and inhibitory domains, thus creating a wide range of clinical conditions. Synthetic cannabinoids are a chemically heterogeneous group of compounds. Similar to natural cannabinoids, they act as agonists of cannabinoid receptors (CB), mainly CB1, producing psychoactive effects. Synthetic cannabinoids exhibit a broad spectrum of clinical effects, which typically occur immediately after inhalation or insufflation and may last from several hours to days, depending on the specific compound and its potency. The signs of intoxication vary according to the substance involved. The involvement of other receptors and enzymes remains to be clarified

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but may include serotonin and N-methyl-D-aspartate (NMDA) receptors, as well as inhibition of monoamine oxidase. However, synthetic cannabinoids have a high potential for severe toxicity. Based on the limited data currently available, the frequency of clinical signs or symptoms following exposure to a single synthetic cannabinoid in 277 reported cases (2010–2015) was as follows:

Agitation, coma, toxic psychosis, or other neurological manifestations (e.g., seizures, hallucinations): 66%
Bradycardia, tachycardia, or other cardiovascular symptoms: 17%
Rhabdomyolysis: 6%
Respiratory depression: 5%
Acute kidney injury: 4%

Neurological outcomes such as severe psychomotor agitation, psychosis, seizures, hallucinations, delirium, dystonia, and paranoia have been documented in several clinical reports and case series. Routine urine drug screening tests often fail to detect synthetic cannabinoids, as their chemical structures and metabolites do not cross-react with delta-9-tetrahydrocannabinol (THC) assays and may therefore remain undetected. Confirmatory laboratory testing through liquid chromatography and mass spectrometry is available but is not performed on an emergency basis and thus does not aid immediate diagnosis. When residues of the ingested substance are available, they may be analyzed by forensic laboratories in collaboration with local authorities. However, given the continuous evolution of chemical structures, even reference laboratories may encounter difficulties in identification (1,2). Another widely used class of NPS includes synthetic cathinones, beta-ketone analogues of amphetamines. Abuse of these compounds emerged in Europe in 2009 and spread to the United States in 2010. They were initially marketed as "bath salts" or "fertilizers" to circumvent regulation under the U.S. Controlled Substances Act. Our understanding of the pharmacodynamics of synthetic cathinones is limited, though specific actions are known for some compounds: methylone and pyrovalerone inhibit norepinephrine and dopamine reuptake with minimal effect on serotonin, whereas mephedrone predominantly inhibits dopamine reuptake. Use of synthetic cathinones produces a prominent neuropsychiatric syndrome characterized by agitation (approximately 82%), aggression (57%), hallucinations (40%), paranoia (36%), confusion (34%), myoclonus (19%), and, rarely, seizures. Most synthetic cathinones are not detected by routine urine drug screens. Some laboratories have successfully identified these compounds using gas chromatography–mass spectrometry; however, such tests are not routinely available, and turnaround times are often incompatible with emergency settings. Delirium is often a symptom associated with both occasional use of these substances and a consequence of withdrawal symptoms. For example, since the latest-generation benzodiazepines have not been tested according to scientific standards, we don't really know what their true effects are. Since they are often derivatives of commercially approved benzodiazepines for therapeutic purposes, and given their likely shared mechanism of action, it's reasonable to assume that these substances also cause addiction, tolerance, and dependence. Therefore, these assays are generally reserved for medicolegal purposes. Synthetic cathinones differ from traditional amphetamines in that their symptoms often persist for many hours or even days; in severe cases, psychiatric manifestations and movement disorders may last for days or weeks after ingestion (3). From these observations, it is evident that cognitive impairment secondary to NPS intoxication is frequently misdiagnosed. Screening for such substances would therefore be advisable in all patients presenting with excitatory or inhibitory neuropsychiatric symptoms, particularly during the early hours of hospital admission. The lack of comprehensive testing, coupled with the continuous introduction of new molecules into the market, hinders precise characterization of their short- and long-term effects. Another major limitation concerns laboratory detection: there are no universal screening tests for all available NPS, and only a limited number of healthcare facilities are equipped to perform such analyses. We believe that the potential effects of NPS in patients with coma should be considered as an independent factor contributing to delayed or altered awakening. NPS may play a critical role in cases of delayed emergence not attributable to organic, iatrogenic, or hydroelectrolytic causes. Delayed

awakening or an alteration in consciousness often has significant implications, not only for the patient, due to worsening prognosis, prolonged hospitalization, and increased risk of infections and complications, but also for public health, as the prolonged intensive care and increased resource allocation required by these patients leads to a consequent increase in healthcare costs in an often already critical context. We therefore propose that the impact of NPS in comatose patients, though still poorly studied, warrants updated preventive and diagnostic approaches across emergency healthcare networks. A potential protocol could involve Point-of-Care Testing (POCT) screening, a method capable of detecting multiple substances, including novel compounds, in different biological matrices (blood, urine, saliva) within timeframes compatible with emergency care. Such screening could be extended to all patients aged 15–55 years presenting to the emergency department with altered consciousness. Another valuable proposal would be to involve Poison Control Centers, which possess specific expertise in intoxication management and maintain direct contact with national and international drug monitoring authorities. This collaboration could provide clearer insight into the problem, offering both immediate clinical benefit and essential data for preventive strategies. It is therefore crucial for healthcare institutions to promote the study of this emerging phenomenon, implementing training programs for the management of NPS-related intoxications, in order to mitigate their significant impact on public health (4,5).

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