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REVIEW ARTICLE

Novel Psychoactive Substances (NPS): Analytical Challenges, Public Health Impact, and Forensic Response in Low and Middle-Income Countries

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ABSTRACT

New psychoactive substances (NPS) are chemically varied substances made to look like controlled drugs but not break the law. Their rapid emergence, unknown challenges pose growing public-health and forensic problems worldwide, including in Low and middle-income countries (LMICs). To evaluate the existing knowledge regarding NPS chemistry and epidemiology, analytical and laboratory challenges, public health implications, and applicable forensic responses pertinent to LMIC contexts, while proposing practical strategies to enhance surveillance, detection, and response. Narrative synthesis of global monitoring reports, technical updates, and peer-reviewed literature concentrating on NPS trends, analytical techniques, surveillance, and forensic casework, particularly in LMICs. Health effects can be anything from severe intoxication and psychosis to death when using very strong synthetic opioids or contaminated supplies. Forensic response in LMICs is limited by resource deficiencies; however, various pragmatic strategies, including regional networks, targeted LC–MS workflows, and shared spectral resources, can significantly enhance detection and public health initiatives. Investing in analytical methods that can be used on a large scale and are cost-effective, as well as working together with other regions, will make it more likely that new threats will be found, and that illness and death will be avoided.

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KEYWORDS

• Novel psychoactive substances • Low and middle-income countries • Toxicology • Analytical detection • Public health

INTRODUCTION

Novel psychoactive substances (NPS) are a group of compounds that are always changing. They include synthetic cannabinoids, cathinones, phenethylamines, benzodiazepine analogues, synthetic opioids (including nitazenes), and others psychoactive effects while evading legal restrictions. Since the middle of the 2000s, their number and variety have grown quickly, making it hard to analyze, treat, and make policies.[1-3] A lot of the data comes from rich countries, but LMICs are reporting more and more NPS use, overdoses, and forensic cases, even though they often don't have enough labs or surveillance to deal with them.[1,17] This review compiles recent monitoring data and methodological literature, underscores challenge pertinent to LMICs and provides practical forensic and public health recommendations.[1,3,10]

Scope and epidemiology of NPS

International monitoring (UNODC, EMCDDA) has recorded hundreds to over a thousand distinct NPS entries since its inception; the overall monitored pool and the substance patterns fluctuate annually.[1–4,6,7,19] The EMCDDA has been keeping track of more than 900–950 NPS in Europe in recent years. The number of new detections changes from year to year, and in some years, most of the major seizures are of a few types of cathinones and ketamine.[3,4,6] UNODC keeps track of and sends out technical updates about NPS classes, health risks, and trends in different parts of the world.[1,2,7,19] The annual number of first-reported NPS has sometimes gone down (because of changes in supply and laws), but the risk to public health is still there because a few very strong drugs (like new synthetic opioids) can cause a lot of harm.[7,10,14] LMICs report a growing occurrence of NPS; however, surveillance is inconsistent and probably underrepresents actual prevalence.[1,13,17] Chemical classifications, impacts, and forensic significance. NPS encompass various chemical families characterized by unique mechanisms and toxicological profiles, including synthetic cannabinoids (cannabinoid receptor agonists) and synthetic cathinones (stimulant-like action), synthetic opioids (mu-opioid agonists, including fentanyl analogues and nitazenes), novel benzodiazepines, and hallucinogenic phenethylamines/tryptamines.[1,5,9,14] Certain categories (synthetic opioids, potent cannabinoids) present significant risks due to their extreme potency, unpredictable adulteration, and variable pharmacokinetics, which hinder postmortem analysis.[5,9,14,15] The ongoing structural alterations by covert chemists (minor modifications to substituents, chain length, stereochemistry) constitute a significant factor in the challenges of analytical detection.[1,8,9,15]

Effects on public health in LMICs

In low and middle-income countries, NPS-related harms include acute intoxications that lead to seizures, severe agitation, respiratory depression (especially with strong opioids), and deaths that can't be explained.[10,13,14,17] For some classes of NPS, there have been reports of psychiatric sequelae, such as acute psychosis and suicidal thoughts.[5,14] Monitoring and case ascertainment are constrained by insufficient awareness, inadequate laboratory validation, and conflicting health system priorities.[1,10,17] These gaps make it harder to recognize outbreaks and make harm-reduction measures (like giving out naloxone and sending targeted messages) less effective.[1,10,20] Case reports and limited studies suggest that NPS-related clusters in LMICs may remain unrecognized for extended durations.[13,17]

Forensic labs: Analytical issues:

- **Main problems with analysis and operations:** Chemical diversity and quick emergence. The wide range of possible structures means that screening methods need to cover a lot of ground and libraries need to be updated often.[1,9,12,15]
- **No reference standards:** Numerous novel substances emerge prior to the availability of certified standards, thereby complicating confirmation and quantification.[9,12]

- **Tools and equipment:** High-resolution mass spectrometry (HRMS) and tandem LC–MS are great for broad screening and figuring out structures, but many labs in Low and middle-income countries (LMICs) don't have these tools or can't afford to keep them up or buy reagents.[12,15,17]
- **Problems with the matrix and metabolites:** Parent compounds can be unstable or highly metabolized; detection windows vary by matrix (blood, urine, hair), requiring validated metabolite panels and alternative matrices for retrospective detection.[9,13]
- **Interpreting data:** Postmortem redistribution, co-intoxicants, and insufficient toxicodynamic understanding impede the determination of the cause of death.[5,8,15,20] These limitations are exacerbated in LMIC contexts where staffing, instrument availability, and supply chains for consumables may be inconsistent.

  Pragmatic, resource-sensitive workflows are thus essential.[12,13,17] Pragmatic laboratory methodologies and workflows tailored for LMICs. There are a few practical ways to improve detection without fully deploying HRMS right away. One is to use validated targeted LC–MS/MS panels for the most relevant NPS classes (synthetic opioids, cannabinoids, and common cathinones) along with an algorithm to send samples to HRMS in sentinel/clinical reference labs. This strikes a balance between cost and coverage.[15,18]
- **Utilization of collective spectral Libraries and open data:** Being a part of regional/shared spectral databases (national/regional forensic networks) speeds up the time between first detection and identification; open repositories and collaborative sharing are necessary.[1,2,12]
- **Alternative sample matrices:** Hair and nails can prolong detection windows for epidemiological surveillance; postmortem matrices and vitreous humour may facilitate interpretation in decomposed bodies. Validation studies tailored to local requirements should be prioritized.[9,13]
- **Cost-effective instrumentation choices:** HRMS is the best choice, but modern triple-quadrupole LC–MS/MS instruments can accurately measure many NPS and their metabolites if the panels are kept up to date. Investing in maintenance and staff training pays off big time.[12,13,15] There have been reports of successful stepwise validation and broad LC–MS/MS panels, showing that they can be used in forensic cases when used correctly.[18,15,13]
- **Surveillance, reporting, and early warning:** LMIC priorities Effective detection of NPS threats requires combining forensic laboratory capacity with public-health surveillance: Sentinel clinical and forensic sites (emergency departments, centralized forensic labs) should report unexplained intoxication clusters rapidly.[10,13,17]
- **Linking to national and regional early warning systems (EWS):** LMICs should connect to global platforms (UNODC EWA, regional alternatives) and share anonymous seizure and spectral data to speed up recognition.[2,19]
- **Syndromic surveillance and toxicovigilance:** Clinical syndromic patterns, such as respiratory depression and severe sympathomimetic toxicity, can prompt targeted analytical testing prior to the availability of a precise chemical identification.[10,17,20] Collaboration among regions, standardized reporting templates, and regular training for doctors and coroners are cost-effective steps that have a big effect.[17,20] Forensic interpretation and medicolegal factors, it is still important to use clinical and scene data to understand toxicology results. In low and middle-income countries (LMIC), a lack of case background information, quality-assured reference ranges, and expertise in NPS toxicodynamics makes it harder to figure out the cause of death.[15,17,20] Strategies to facilitate interpretation encompass multidisciplinary mortality review panels, standardized case report forms documenting product source and packaging, and the employment of conservative language in medicolegal reporting when attribution remains uncertain.[8,17,20] Policy, legal frameworks,

and harm-reduction considerations: Clandestine chemists can outpace rigid single-compound scheduling. LMICs ought to contemplate adaptable legal instruments (generic, analogue, or emergency scheduling) in conjunction with public health initiatives (availability of naloxone, poison control assistance, harm reduction communication).[14,16,20] Legal measures necessitate concurrent investments in forensic and clinical services; mere criminalization, devoid of detection and treatment capabilities, may exacerbate harm.[1,14,20] Recommendations (practical, LMIC-focused): Set up tiered analytical workflows by building regional reference centers with HRMS and giving peripheral labs targeted LC–MS/MS panels.[15,18,17] Put money into shared spectral libraries and data sharing: sign up for international Early Warning systems and make deals to share data in your area.[2,12,19]

- **Training and retention first:** laboratory method validation, QA/QC, and teaching clinicians how to spot NPS presentations.[17,20] Use flexible legal and regulatory systems to allow for quick control when needed, along with harm-reduction strategies.[14,16,20] Put sentinel syndromic surveillance into action in emergency rooms and forensic services to quickly find clusters.[10,13,17,20]

Constraints and research deficiencies

Data from numerous LMICs are still limited, and publication bias tends to favor significant events or regions with enhanced capacity. There are still gaps in research, such as the need for standardized postmortem interpretation for many NPS, population pharmacokinetic data, validated metabolite markers, and cost-effective, field-deployable screening tools that are appropriate for LMICs.[13,15,20] Future endeavors ought to concentrate on these domains and on operational research aimed at scalable solutions.[13,15]

CONCLUSION

Novel psychoactive substances (NPS) remain a significant and evolving public health threat worldwide, especially affecting Low and middle-income countries (LMICs). These areas often have trouble with not enough laboratory space, not enough resources, and gaps in surveillance, which make it hard to find problems quickly and act. But, by making smart, practical investments, you can make a lot of progress. Using tiered laboratory workflows makes the best use of the resources that are already there, while working together and sharing data across regions encourage group learning and quick action when new threats come up. Involving clinicians in the surveillance and response process and using flexible policy frameworks that find a balance between regulatory control and harm-reduction principles are also very important parts. By putting these approaches first, LMICs can improve both public health and forensic readiness for NPS challenges. In the end, coordinated action between pertinent sectors will expedite detection, facilitate targeted interventions, and markedly diminish morbidity and mortality linked to the continually changing realm of NPS.

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