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Review Article

New Psychoactive Substances: A Potential Threat to Developing Countries

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Abstract

Background: New psychoactive substances (NPS) have become a global phenomenon, with over 134 countries and territories from all world regions reporting them. Since December 2021, governments, laboratories, and partner agencies have confirmed to the UNODC Early Warning Advisory (EWA) on NPS over 1124 substances. It is agreed that NPS control is one of the most challenging tasks for developing countries. Identifying the present and future threads of NPS is the most challenging task for law enforcement officials. The NPS research has a great impact on substance abuse policy-making and harm reduction strategies.

Methods: The data in this study were collected from the official websites of online journals, Google Scholar, UNODC, International Narcotics Control Board (INCB), and the Department of Narcotics Control (DNC).

Findings: Among the eleven groups of NPS, synthetic cannabinoids and cathinones are the most prevalent and alarming in developing countries. In Bangladesh, NPS abuse has been first identified in 2016. Almost 60 countries adopted legislative solutions to manage NPS by 2021, with many using or amending existing legislation and others employing novel legal mechanisms. It is widely agreed by researchers that reducing the menace of NPS requires increased awareness among all stakeholders.

Conclusion: In the fight against the spread of NPS and its severe effects, law enforcement authorities and healthcare professional training must be seen as crucial aspects as well. Financing is also crucial for international organizations dealing with the NPS impact to continue fighting this war. The only way for policymakers to reduce NPS spread globally is through national and international cooperation.

Keywords: New psychoactive substances, Developing countries, Drugs, UNODC, Bangladesh

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Introduction

New psychoactive substances (NPS) are emerging as a problem for public health. NPS have been referred to in the market as "research compounds", "legal highs", and "bath salts".[1] Similar effects can be produced by these compounds as by conventional medications or by drugs that have already been created but are being employed in novel ways. NPS are described by the United Nations Office for Drugs and Crime (UNODC) as the substances "that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat" and as "substances of abuse, either in a pure form or a preparation".[2] Although several NPS were initially synthesized decades ago, the phrase "new" refers to chemicals that have only recently become commercially available. It does not always allude to recent inventions.[3]

NPS are reportedly present all over the world, according to media sources. The market expansion is also leading to an increase in the use of NPS besides many other classic illegal substances including heroin, cannabis, and opium. With over 134 countries and territories reporting NPS abuse, the UNODC remarked that NPS have grown into a global phenomenon. Up till December 2022, more than 1124 compounds have been listed in the UNODC Early Warning Advisory (EWA) on NPS by various partner organizations.

This review study aimed to (I) highlight the prevalence of NPS in countries like Bangladesh and other developing nations and (II) investigate the need for additional research on NPS that would facilitate policy-making.

Methods

To find articles that examined NPS and other non-conventional drugs in developing countries, the authors searched a number of journals as well as the official websites of the Department of Narcotics Control (DNC), International Narcotics Control Board (INCB), the EWA on NPS, UNODC on NPS, and Google Scholar.

Results

Classification

As per UNODC EWA, the main classes of NPS are:

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Aminoindanes

The aminoindanes were said to have strong analgesic and bronchodilating activities in the 1970s significantly affecting both serotonin release and reuptake.[4] These substances have been promoted as NPS due to their ability to mimic the empathogenic and entactogenic effects of serotonin-releasing drugs like MDMA. Two types of aminoindanes structures are shown in Figure 1.

Synthetic cannabinoids

It is not a recent phenomenon for "herbal highs" to arrive on the market. Typically, these products were plant combinations with minimal psychotropic effects.[5] However, it appears that the formulas of these herbal medications have significantly changed since 2004 to incorporate powerful brand-new synthetic cannabis compounds.[6]

Several decades ago, when compounds with behavior resembling that of 9-tetrahydrocannabinol (THC) were initially investigated, research on the mechanism of cannabis activity began to emerge. The first synthetic version of THC, known as "HU-210", was created in Israel in 1988, and its potency is thought to be at least 100 times greater than that of THC.[7] Due to the fact that "HU-210" shares a chemical structure with THC, it is regarded as a "classical cannabinoid" and has been found in synthetic cannabinoids that are sold in the United States and other countries.[8] Three types of synthetic cannabinoids structures are shown in Figure 2.

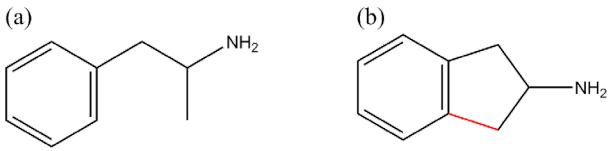

Figure 1. (a) amphetamine (b) 2-aminoindane (2-AI)

Synthetic cathinones

Chemically identical to amphetamine and methamphetamine, synthetic cathinones are "β-keto phenethylamines". Cathinone, the principal active component of khat (*Catha edulis*) leaves, can be viewed as the template from which other synthetic cathinones have been developed.[9]

In the middle of the 2000s, synthetic cathinones first arrived on the drug market. In 2005, methylone, an MDMA homologue, was the first synthesized cathinone reported to the European Monitoring Center for Drugs and Drug Addiction.[10] Reports of the use of 4-methylmethcathinone (mephedrone) began to surface in 2007, first in Israel, then in several other nations and regions, including Australia, Scandinavia, Ireland, and the United Kingdom. According to reports, mephedrone was originally created in 1929.[11] Six types of synthetic cathinones structures are shown in Figure 3.

Phencyclidine-type substances

Phencyclidine (PCP)-type substances are categorized as arylcyclohexylamines and share structural similarities with PCP and ketamine.[12] In the United States, PCP was originally produced in the 1950s and was marketed as an injectable anesthetic under the brand names Sernyl and Sernylan until 1967. Due to extremely detrimental psychological side effects such as dysphoria, confusion, delirium, and psychosis, it was taken off the market. Midway through the 1960s, it became popular as a recreational drug, but its unexpected dysphoric side effects made it notorious. The 1971 Convention, Schedule I regulates PCP and its phenyl cyclohexyl analogs, while schedule II regulates methoxetamine (MXE)

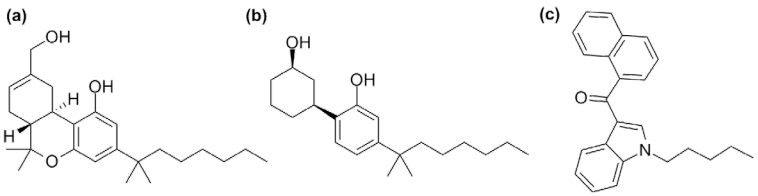

Figure 2. (a) classical cannabinoid (b) non-classical cannabinoid (c) aminoalkylindoles

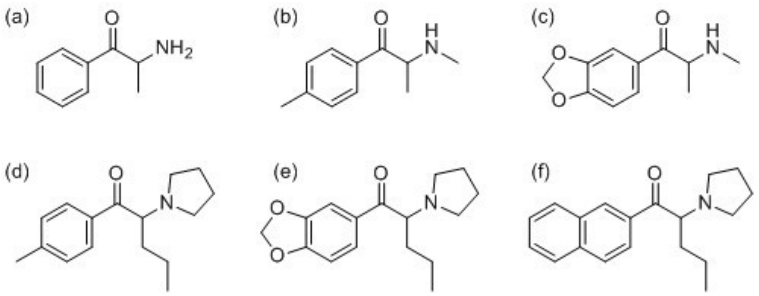

Figure 3. Synthetic cathinones: (a) cathinone, (b) 4-methylmethcathinone, (c) methylone, (d) pyrovalerone, (e) 3,4-methylenedioxypyrovalerone, (f) naphyrone

but its derivatives like 3-MeO-PCE are not subject to transnational regulation.[13]

Phenethylamines

The 1971 Convention regulated the category of drugs known as phenethylamines which have been shown to have established psychotropic and stimulant properties.[14] Phenethylamine seizures were originally noted in the United States and Europe, and since 2009, other nations in various areas have regularly reported seizures of these compounds.[15] According to several investigations, a number of phenethylamines and amphetamine replacements have been synthesized.[16] Alexander Shulgin, a scientist and pharmacologist, reported the synthesis of various NPS in the 1980s and 1990s. These include phenethylamines of the "2C series" and "D series" such as 2C-T-7.[17]

Piperazines

Since some piperazines had been considered by pharmaceutical corporations as potential medicinal agents never released on the market, they have been referred to as "failed pharmaceuticals". Although other piperazine compounds have also been identified, 1-benzylpiperazine (BZP) is a kind of piperazine that has been frequently utilized as NPS .[18] Three types of piperazines structures are shown in Figure 4.

Plant-based substances

The Gulf Region and the African Horn are the native habitats of khat shrub (*Catha edulis*). Khat chewing is a common social practice in the local populations. After chewing khat, cathinone and cathine alkaloids are released causing euphoric effects that have been extensively studied.[19]

A sizable tree belonging to the Rubiaceae family called *Mitragyna speciosa* Korth is found in the tropical and subtropical areas of Southeast Asia. Despite the fact that it is illegal to cultivate and harvest the "kratom" tree, it is widely distributed throughout the southern part of Thailand.[20]

Tryptamines

Tryptamine and its derivatives, which have been designated as NPS, are among the indole alkylamine group.[21] The majority of naturally occurring tryptamines are psychedelic hallucinogens found in plants, fungi, and animals, while some of them are neurotransmitters (such as serotonin, melatonin, and bufotenin).[22] Three types of tryptamines structures are shown in Figure 5.

Benzodiazepines

Benzene and diazepine ring combine to form a molecular core of benzodiazepines, a class of psychotropic medicines. These are used as depressants to treat problems like anxiety, sleeplessness, and seizures by reducing brain activity.[23] Leo Sternbach made the first benzodiazepine, chlordiazepoxide (Librium), unintentionally in 1955. Hoffmann-La Roche made it commercially available in 1960, and diazepam (valium) was released shortly after. Benzodiazepines were the most frequently prescribed medications worldwide by 1977. Benzodiazepines are still frequently used today despite the fact that prescription rates have decreased due to the development of selective serotonin reuptake inhibitors, among other factors.[24]

Fentanyl analogs

A very potent synthetic narcotic called fentanyl is mostly used to lessen the suffering of people with terminal conditions or chronic pain.[25] The medication has been marketed as a patch or lozenge since the 1990s for optimizing the delivery of time-released medications to enhance efficiency.[26] Due to the potent nature of fentanyl, there is a hypothesis that residual chemicals from used patches may pose a risk of contaminating water systems if flushed down the toilet.[27] Additionally, it has happened that used patches have stuck to kids or animals, leading to unintended overdoses.[28]

Other substances

Some NPS compounds, such as 1,3-dimethylamylamine (DMAA), have a variety of structural characteristics

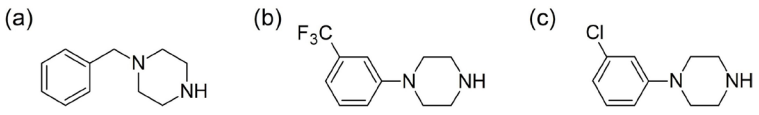

Figure 4. (a) 1-benzylpiperazine (b) 1-(3-trifluoromethylphenyl) piperazine (c) 1-(3-chlorophenyl) piperazine

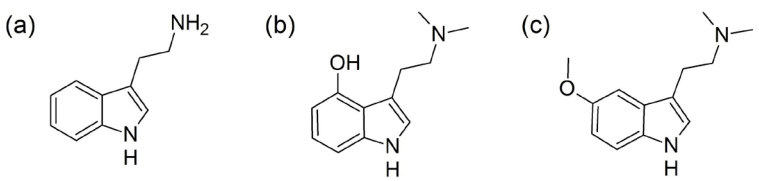

Figure 5. (a) tryptamine, (b) psilocin, and (c) 5′-methoxy-N, N-dimethyltryptamine

and do not fall into the categories listed above.[29] Classic hallucinogens (psychedelics), which mediate specific serotonin-receptor responses and result in hallucinations, are just one of the many pharmacological effects that these drugs have. These substances imitate the effects of conventional drugs like 2C-B, LSD, and DMT, but they may also still have some strong stimulant activity.[30]

Opioids are central nervous system depressants that are chemically varied. They possess structural characteristics that enable binding to particular opioid receptors, producing effects similar to those of morphine, such as analgesia.[31]

Hypnotics and sedatives slow down the central nervous system. The benzodiazepines diazepam and alprazolam, which are subject to worldwide regulation, are just two examples of the medications they mimic. They imitate the effects of medications that are subject to international regulation, such as the benzodiazepines alprazolam and diazepam.[32]

Harmful effects

NPS use is frequently associated with health issues. Seizures, agitation, violence, acute psychosis, and potential dependence are just a few of the negative effects of NPS.[33] Heavy intoxications caused by NPS use have often necessitated hospitalization.[34] A substantial number of NPS have limited or insufficient data regarding their safety, toxicity, and potential for causing cancer, and little is known about their long-term hazards or negative consequences. The purity and composition of some NPS are unknown, putting users at grave risk, as evidenced by hospital emergency admissions and deaths linked to NPS, frequently including cases of polysubstance use.[35]

A few different pharmacological pathways are used by the chemicals regulated by international drug conventions to produce psychoactive effects.[36] Examples include altering the levels and activities of the monoamine neurotransmitters dopamine, adrenaline, and serotonin; functioning as an N-methyl-D-aspartate receptor antagonist; activating the cannabinoid receptor type 1 (CB1); acting on the GABAA receptor to generate sedative, hypnotic, and anxiolytic effects; and interacting with opioid receptors and inhibitory neurotransmitters.[37,38]

Potential threats

NPS are spreading at an incredible rate, endangering public health and complicating drug policy-making.[39] The negative health impacts and social harms of NPS are frequently poorly understood, which makes prevention and treatment extremely difficult. To combat this new drug issue, monitoring, information sharing, and risk awareness are required.[3]

The internet today allows NPS to spread quickly, making it challenging for law enforcement organizations to immediately detect and control drugs. The very first phase of the investigation i.e., identification of a suspect of drug abuse, is disrupted by its stability. The main problem for law enforcement organizations is the lack of understanding of NPS. One way to describe new psychoactive chemicals is as a complex topic that is always changing and has a plethora of specific details that might mislead all experts.[40]

Furthermore, there are little or no public awareness initiatives that could spread fundamental information concerning NPS. Accordingly, law enforcement officials frequently rely on the web as their main source of knowledge about NPS, including its chemical structure, producer locations, distribution strategies, and end-user demographics.[41]

Current situation of Bangladesh

In the last 10 years, the use and abuse of novel psychoactive chemicals, also known as "legal highs", have rapidly expanded throughout the world. The NPS problem has been recognized in Bangladesh since 2018 and has become important due to the geographical location of the country. The Golden Triangle and Golden Crescent have made NPS trafficking and drug abuse more prevalent in the country. Besides, the pharmacy and drug regulatory systems in Bangladesh are patient-friendly. Thus, malpractices like 'prescription hopping' are a common modus operandi followed by abusers to procure controlled drugs from pharmacies. Abusers also misuse the prescriptions of their family members, friends, etc. to obtain drugs, and some of them resort to "doctor shopping" i.e., procuring prescriptions from multiple doctors to procure controlled drugs from pharmacies.

All attempts to infiltrate the newly formed NPS are traced through the implementation of a complete action plan in accordance with the guidelines. As a result, for the first time, plant-based NPS khat was seized in Bangladesh in 2018. Totally, 4.5 metric tons of khat were seized at Dhaka and Chattogram airports and considerable amounts of LSD and MDMA were seized in 2019. Phenethylamine, an organic substance, was seized in 2020, psilocybin mushrooms were seized in 2021, and DOB and kratom plants were also seized in 2022 (Table 1). As the method of operation is similar to that of ATS, locally-made tapentadol HCl is abused instead of ATS. Its use and promotion are similarly regulated. The capacity of law enforcement agencies and transportation employees has expanded. As a result, no attempt to access NPS has succeeded at any time or in any form. With the collaboration of the mass community, drug pharmacists, physicians, and other national and international authorities, the DNC has been able to successfully monitor and regulate the overall situation.

Country-wise distribution

In India, 33 NPS-related incidents have been reported since

Table 1. Detailed NPS seized in Bangladesh

No. of Incidents	Year	Substance Name	Abbreviation	Alternative Name	Class
13	2018	Khat		Catha edulis	Plant-based substances
5	2019	Lysergic acid diethylamide	LSD		Other substances
2	2019	6-bromo MDMA	MDMA		Phenethylamines
2	2016	Phencyclidine	PCP	Ketamine	Phencyclidine-type substances
1	2022	Kratom		Mitragyna speciosa	Plant-based Substances
1	2020	1-phenylethan-1-amine		Phenethylamine	Phenethylamines
1	2022	Dimethoxybromoamphetamine	DOB		Phenethylamines
1	2021	Psilocybin		Magic Mushroom	Other substances

2009 among which ketamine, 4-methylmethcathinone (4-MMC), 3-methoxyeticyclidine (3-MeO-PCE), etizolam, and khat are noticeable.

In Thailand, ketamine, etizolam, kratom, 1-(3-Trifluoromethylphenyl)piperazine, phenazepam, M-alpha, diclazepam, 3,4-methylenedioxypyrovalerone, JWH-018, ethylone, khat, ((±)-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-N,N,3-tri methyl butan-1-amine, methylone, 2-[3-(aminomethyl)-5-methyl-4H-1,2,4-triazol4-yl]-5-chlorophenyl-((phenyl)methanone, 3,4-methylenedioxy-N,N-dimethylcathinone, para-methoxymethamphetamine (PMMA), para-methoxymethamphetamine, 1-(3-chlorophenyl) piperazine, 3-Methoxyeticyclidine (3-MeO-PCE),7-[2-([1-(4-chlora-2,5-dimethoxyphenyl)propan-2-yl]amino) ethyl]-1,3-dimethyl-3,7 dihydro-1H-purine-2,6-dione, 4-methylmethcathinone (4-MMC), N-benzylpiperazine (BZP), 1,4-dibenzylpiperazine (DBZP), flunitrazolam, XLR-11, alpha-pyrrolidinovalerophenone, beta-keto-N-methylbenzodioxolybutanamine, and isopropylphenidate were seized in a total of 66 incidents.

In Indonesia, a total of 129 incidents are documented among which, 1 is related to benzodiazepines, 43 to synthetic cannabinoids, 28 to synthetic cathinones, 20 to PCP-type substances, 13 to phenethylamines, 11 to piperazines, 8 to plant-based substances, 1 to tryptamines, 1 to fentanyl analogues, and 3 are related to other substances.

In Malaysia a total of 162 incidents are described among which 13 incidents are related to benzodiazepines, 45 to synthetic cannabinoids, 38 to synthetic cathinones, 21 to PCP-type substances, 2 to phenethylamines, 21 to piperazines, and 19 to plant-based substances.

In China, 446 incidents are reported among which 3 are related to aminoindanes, 10 to benzodiazepines, 129 to synthetic cannabinoids, 148 to synthetic cathinones, 37 to PCP-type substances, 11 to phenethylamines, 8 to piperazines, 7 to plant-based substances, 15 to tryptamines, 20 to fentanyl analogs, and 24 are related to other substances as listed in the UNODC EWA.

In Turkey, 959 incidents are reported among which 1 is related to aminoindanes, 5 to benzodiazepines, 640 to synthetic cannabinoids, 119 to synthetic cathinones, 12 to PCP-type substances, 64 to phenethylamines, 31 to piperazines, 38 to plant-based substances, 21 to tryptamines, 1 to fentanyl analogs, 27 to other substances as listed in the UNODC EWA.

In Argentina, 107 incidents are reported among which 11 are related to synthetic cannabinoids, 26 to synthetic cathinones, 12 to PCP-type substances, 37 to phenethylamines, 1 to piperazines, 9 to plant-based substances, 6 to tryptamines, 1 to fentanyl analogs, and 4 to other substances as listed in the UNODC EWA.

In Brazil, 416 incidents are reported among which 1 is related to aminoindanes, 2 to benzodiazepines, 640 to synthetic cannabinoids, 119 to synthetic cathinones, 15 to PCP-type substances, 148 to phenethylamines, 6 to piperazines, 4 to plant-based substances, 20 to tryptamines, 5 to fentanyl analogs, and 26 to other substances as listed in the UNODC EWA.

In Egypt, 25 NPS-related incidents have been reported since 2009 among which khat, alpha-methyltryptamine, methylone, ketamine, ayahuasca, kratom, 2-aminoindane, and alpha-pyrrolidinovalerophenone are noticeable.

In South Africa, 21 NPS related incidents have been reported among which khat, N-benzylpiperazine, 4-benzylpiperazine, salvia, 2-diphenylmethylpiperidine, ketamine, and JWH-018 are noticeable.

In Bulgaria, 337 incidents are reported among which 2 are related to aminoindanes, 2 to benzodiazepines, 172 to synthetic cannabinoids, 69 to synthetic cathinones, 10 to PCP-type substances, 29 to phenethylamines, 5 to piperazines, 16 to plant-based substances, 9 to tryptamines, 1 to fentanyl analogs, and 22 to other substances as listed in the UNODC EWA.

In Hungary, 879 incidents are reported among which 6 are related to aminoindanes, 11 to benzodiazepines, 301 to synthetic cannabinoids, 283 to synthetic cathinones, 43 to PCP-type substances, 88 to phenethylamines, 8 to piperazines, 10 to plant-based substances, 27 to tryptamines, 8 to fentanyl analogs, and 94 to other substances as listed in the UNODC EWA.

Measures taken by countries

Since NPS are not controlled by the international drug

control conventions, their legal status could very well vary widely from country to country. More than 60 countries put legal measures in place to regulate NPS, with many of those using or amending already-existing law while others using cutting-edge legal tools. Numerous nations, where a diverse array of NPS originated, have implemented controls on entire NPS groups using a so-called generic approach or have introduced analogous legislation that uses the concept of "chemical similarity" to an already-controlled substance to regulate substances that are not specifically mentioned in the legislation. The Commission on Narcotic Substances voted to place 68 NPS under global international control until March 2021.

Future prospects

The Director General of the DNC has developed a comprehensive action plan. Under this approach, the narcotics control act of 1990 was repealed and replaced by the narcotics control act of 2018. This act has incorporated new facets or dimensions of the NPS problem, such as LSD, DOB, MDMA, Magic Mushroom, phenethylamine, khat, tapentadol HCl, tramadol, nalbuphine, oxymorphone, and others. The temporary probationary period for newly emerging NPS is preserved. This control measure is only in place because of the legal structure at the national level. The severity of the penalty and punishment has increased and the airport, seaport, and land port have all been upgraded. Moreover, the inspection of local pharmacies and drugs has been intensified and a technical session for clinicians was held to restrict the prescription of these medications. DNC has undertaken a number of NPS training programs as part of its capacity-building operations for law enforcement agencies and transportation-related personnel. It is necessary to expand the digitalization of medicine marketing and its monitoring system.

Discussion

The use of NPS is a global public health threat, and Bangladesh is not an exception. The geographical location of Bangladesh has made it vulnerable to drug trafficking and abuse. Additionally, the patient-friendly pharmacy and drug regulatory systems in the country have made it easy for abusers to obtain controlled drugs through malpractices. The DNC in Bangladesh has developed a comprehensive action plan to tackle the issue of NPS, which includes repealing and replacing the existing Narcotics Control Act of 1990 with the Narcotics Control Act of 2018.

The new act includes new areas of the NPS issue such as LSD, DOB, MDMA, Magic Mushroom, phenethylamine, Khat, Tapentadol HCl, Tramadol, Nalbuphine, and others. The plan also includes several measures such as increasing the severity of penalties and punishment, upgrading airport, seaport, and land port inspections, intensifying inspections of local pharmacies and drugs, restricting prescription of these medications through technical sessions with clinicians, and undertaking NPS training programs for law enforcement agencies and transportation-related personnel. Moreover, the DNC has called for the expansion of the digitalization of medicine marketing and monitoring systems.

The present study also provided information on the distribution of NPS-related incidents in various countries. The reported incidents vary from country to country, but synthetic cannabinoids and cathinone are the most commonly seized NPS groups. Ketamine, Etizolam, Khat, and Kratom are some other noticeable substances reported in different countries.

The growing problem of NPS use and misuse is a global public health issue that requires a comprehensive response from law enforcement agencies, healthcare professionals, and policymakers. The action plan developed by DNC in Bangladesh is a step in the right direction, but sustained efforts and collaboration are necessary to address this challenge effectively. Furthermore, international cooperation and information sharing among countries could be beneficial in combating the illicit production and trafficking of NPS.

Conclusion

From the point of view of physicians, easy access, availability, and affordability are believed to be the main reasons leading to NPS abuse in developing countries. They also agreed that the self-medication of pharmaceutical drugs like benzodiazepines often leads to its misuse. The female population is more likely to abuse sedative and tranquilizing drugs. Similarly, people with pre-existing psychiatric conditions are more likely to abuse pharmaceutical drugs. These abusers generally do not seek any medical treatment and they remain as the hidden population of drug abusers.

A comprehensive strategy is required for effective NPS phenomena resolution. The most likely response to the proliferation of NPS is new legislation, which is also essential for drug policy reform. Public safety may be greatly reduced with vigorous communication campaigns and better coordination and collaboration between all stakeholders. In the fight against the development of NPS and its terrible repercussions, LEA and healthcare professional training must be taken into consideration as being of utmost importance. Therefore, the relevant international organizations require funds to continue their activities in the conflict. The additional expenditures will be astonishing if efforts to reduce NPS consumption globally are unsuccessful. The costs of combating addiction, harmful health impacts, and drug-related crimes will far surpass the costs of implementing a redesigned, all-inclusive strategy built on cooperation. The only way for policymakers to reduce the global

spread of NPS is through cooperation.

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Supervision: Shahjahan Ali Sarker.
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