

**DRUG INTERACTIONS IN THE CONSTITUENTS OF STREET DRUG MIXTURE
“NYAOPE” IN SOUTH AFRICA: A MINI-REVIEW**

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ABSTRACT

Nyaope is a unique South African street drug mixture thought to contain illicit drugs and other compounds and is usually inhaled after wrapping in the Cannabis leaf. Despite its illegalization in March 2014, abuse of Nyaope is on the increase. While highly addictive, withdrawal symptoms are very severe, unbearable and drive the user to desperately seek for the next fix. Due to the lack of knowledge in its composition and how the constituents interact with each other, treatment for withdrawal symptoms and rehabilitation has been a challenge. A mini-literature review was done to explore how the major constituents of Nyaope relate to each other in their actions and in their path of breaking down (metabolism). The literature suggests that the inside opiate group, in between opiates and benzodiazepines, in between opiates and cannabis group, in between benzodiazepines and phenobarbitals, and also amongst the minor constituents, there are extensively shared the metabolic pathways which lead to longer plasma half-life in each of these drugs and thus synergistic effects. These shared pathways are via the cytochrome P450 family of enzymes in the liver cell cytoplasm and these enzyme actions are to inactivate or detoxify the drugs or convert them to more water soluble compounds in order to excrete them through the kidneys. Not only sharing the metabolic pathways, but also the actions of these drugs at certain receptors in the brain have either opposing or stimulating effects on one another, making the complex nature of their combined actions. Such findings can explain the unique withdrawal symptom complex of Nyaope, which is important for the clinicians and public health workers who are dealing with the users. Understanding the biochemical

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and metabolic basis of Nyaope drug interactions provides valuable insight towards the development of withdrawal signs and symptoms which may contribute to the targeted treatment program.

Keywords: Nyaope, drugs of abuse, withdrawal symptoms, drug synergy, metabolism

INTRODUCTION

Nyaope is a mixture of street drugs commonly used in South Africa mostly consumed by the youth of poor socio-economic background due to its availability and affordability in the townships and informal settlement areas. In the recent years; the use of Nyaope has become a national crisis despite its illegalization in 2014. There have been assumptions that it contains low grade heroin, marijuana, cleaning detergents, rat poison and chlorine, although these cannot be confirmed due to lack of laboratory infrastructure to analyse the mixture and difficulty in obtaining the mixture samples (Tau, 2013). Nyaope is cheap, costing only around Rand 30 (about 2 USD) for one dose and easily accessible at the street corners and vendors in many townships. The Nyaope mixture is a brown coloured powder, thus can be easily disguised as soil or cement powder. This poses difficulty in prosecuting the users especially because they can claim it as a pack of sand or soil since it is common practice in African culture to eat soil. The fact that the laboratories to verify if it is sand/soil or drug mixture are not readily available, the consumers or dealers always get away with processing the mixture. Psycho-social factors such as unemployment, dropping out from school, lack of family and social support, homelessness and peer pressure are

amongst other factors driving the abuse of this drug cocktail (Maseko, 2015).

In the past, laboratory analysis of Nyaope was not available due to difficulties in obtaining specimens as well as the need to have a complex instrument and method to identify the individual component, thus the assumptions of what it may contain were based on the clinical presentation of the users after consumption and during withdrawal period. One study was done to analyse Nyaope samples in Gauteng province of South Africa recently to show the constituents and their patterns across the samples (Khine, Mokwena, Huma & Fernandes, 2015).

Nyaope users present with a unique withdrawal feature of severe unbearable abdominal cramps, but other symptoms and signs are variable from one area to the other. There is no specific medical treatment for the users during withdrawal and rehabilitation. It would be beneficial for the public health practitioners to understand what contributes towards the development withdrawal symptoms complex so that they may improve the medical treatment. This literature review is to explore how the major constituents of Nyaope share their metabolic pathways leading to interactions and synergistic effects that may explain the withdrawal symptoms, which is important for the clinicians and public health workers dealing with the users.

METHOD

This is an unsolicited submission where the researcher believes there is a need to review the available literature to close the gap in knowledge and report the findings. The study is a status quo review of the given topic (drug mixtures and interactions) on the most current and focussed studies which are compared and summarised on the basis of the author's experience and existing theories. Findings are qualitative nature and used to understand the nature of interactions between different drug classes found in the mixture.

The bibliographic databases used were Cochrane library and Google scholar and inclusion criteria were 1) full text articles and studies 2) period from 2003 to 2016 and 3) search words used were; drug mixtures, drugs of abuse, poly drug use, drug synergy, interactions, toxicity and metabolism. Search strategies were 1) using these words separately in the initial search, 2) then again by combining a few of these [e.g. poly drug use and metabolism] [drug synergies and metabolism], 3) lastly by specifying drug classes and combining phrases [e.g. opiates and opioids co-use and metabolism] [opiates and benzodiazepines co-use and metabolism] [central nervous system stimulants and depressants co-use and metabolism] [illicit drugs and alcohol] [hepatic enzyme induction by phenobarbital and alcohol] [poly drug use and withdrawal effects] [poly drug use and toxicity].

There were a few limitations. Since Nyaope is unique to South Africa and due to its recent development, there are no studies done about it especially with respect to its compositions either in the country or in the world literature. Thus other mixtures alike (containing opiates

and alcohol, opiates and benzodiazepines or Phenobarbitals were selected where available) and when literatures for the mixture format was not available, single drugs and their information were used. Moreover, two articles of 1996 were included despite being out of determined period because the information they provide was essential and could not be found in more recent periodicals.

In this review, also included was the important information from the interviews with the actual Nyaope users conducted by the co-author who is a public health practitioner as they may contribute in the understanding of withdrawal symptoms.

LITERATURE REVIEW

Reports on the metabolism of each of the drugs found in the Nyaope mixture is presented together with how the drugs share the enzymes in their metabolic pathway which impact on their blood level and excretion. Reports on the clinical effects of combining different class of drugs of abuse are also discussed. The findings are categorized in the following table and each is elaborated in the texts.

Nyaope constituents

In 2014 the analysis of Nyaope samples was attempted using two Mass Spectrophotometric methods to compare their performance in detecting the constituents. The time of flight mass spectrometry was found to be a faster and more cost-effective method. In this study the Nyaope samples were obtained from various townships and urban areas of Northern Gauteng and Mpumalanga provinces and analysis was done at the Perkin Elmer research laboratory in Midrand

	Findings	Source
1	Nyaope constituents	
	<u>CNS depressants (Major constituents):</u>	
	1) Opiates (Heroin, Codeine, Morphine and Acetyl Morphine, meconin)	Only one study found (Khine, Mokwena, Huma & Fernandes, 2015)
	2) Opioids (Methadone, Papaverine, Dimenoxitol, Benzitramide, thiofentanyl, tramadol)	
	3) Non-opiate CNS depressants (Dextromethorphan, Benzodiazepines, Phenobarbitone)	
	<u>CNS stimulants (Major constituents):</u>	
	Amphetamine, Meth-amphetamine (Kath/crystal meth), Cathine (beta hydroxyl amphetamine), Pipradrol (dopamine and Norepinephrine reuptake inhibitor), Fenelthylline (sympathomimetic bronchodilator).	
	<u>Minor constituents:</u>	
	Acetaminophen, caffeine, antibiotics (citorflex), anti-retroviral (zidovudine), local anaesthetics (duracaine/lidocaine), plasticisers and calcium oxide ground material for binding and stabilisation of drugs.	
2	Metabolism of Nyaope constituents	
2.1	Opiates and opioids shared metabolism via 3 phases of hepatic cytochrome P450 enzyme system in the liver and thus competition of enzymes amongst various drugs in these groups will lead to reduced conjugation and excretion.	Meyer (1996), Dean (2006), Smith (2009),
2.2	Cannabis and tetra hydro cannabis (THC) shared metabolism with opiates and opioids via P450 hydroxylation and oxidation systems.	(Sharma, 2012; Maurer, Saucer, & Theobald, 2006)
2.3	Benzodiazepines and opiates sharing metabolic paths via glucuronidation in the liver. When co-used with Phenobarbital, the latter produces tolerance of the former by inducing glucuronidation enzymes.	Oshiro (2013)
2.4	Phenobarbitals when co-used with opiates, alcohol or benzodiazepines, it stimulates the P450 enzymes for each of these co-used and metabolized them faster than usual leading to tolerance	Meyer (1996)
2.5	Amphetamine and methyl-amphetamine share demethylation pathway with opiates and opioids making their plasma levels higher	Maurer, Kraemer, Springer, & Staack, 2004)
2.6	Minor constituents such as caffeine and acetaminophen (paracetamol) as well as Dextromethorphan, and Lignocaine also shared certain P450 enzymes called CYP3A4 AND 1A2 with opiates and benzodiazepines.	Meyer (1996)
3	Synergies amongst major drug groups in Nyaope	
3.1	Opiates, opioids and benzodiazepines sharing metabolism leads to higher intensity of euphoria and addiction.	Dean (2006)
3.2	Cannabis and THC up-regulate the opiate receptors in brain and potentiates opiate's effect of CNS suppression, hence better pain relief and stronger addiction.	(Cichewicz, 2004; Chimalakonda, Seely, Bratton, Brents, Moran, Endres, & Moran, 2012)
3.3	Benzodiazepines and Phenobarbitals potentiate each other's CNS depressant activities leading to severe drowsiness and disorientation	National Institute on Drug Abuse, 2016
3.4	Amphetamine, Meth-amphetamine, Cathine-beta hydroxyl amphetamine, Pipradrol, and Fenelthylline synergize to give intense euphoria	United States Maine County Law Department, 2010
3.5	cocaine, morphine and heroin, when added with meth-amphetamine, they together cause unbearable and severe abdominal cramps	Tiwari, Moghal, and Meleagrow (2006)
3.6	Paradoxical effects of CNS depressants and CNS stimulants	Wise (1996)
3.7	Combination of anti-retro virals with drugs of abuse	(Pal, Kwatra, Minocha, Paturi, Budda, & Miltra, 2011), Thomas and Velaphi (2014)
3.8	Combination of anti-histamines with opiates	Sandor, 2000

Johannesburg South Africa with the assistance of a technical expert from the company. The details of the components consistently found in Nyaope are listed in the table 1. Rat poison and chlorine, previously thought to be in the mixture were not found in these samples. It was noted that the minor constituents were variable amongst the samples collected (Khine, Mokwena, Huma & Fernandes, 2015).

Metabolism of Nyaope constituents after consumption

Opiates, opioids and non-opiate CNS depressants

The usual way of consumption is by wrapping the drug powder mix in the cannabis leave and smoking it inhaling through the mouth. The plasticiser in the mixture is thought to be enhancing the combustion. How drug residues get into the blood via the oral cavity or respiratory epithelium is now known. There is no study found regarding blood levels of drugs contained in the Nyaope mixture in the users after smoking. However, there are references to explain the fate of constituent drugs in the user's body. The opiates and opioids are metabolised in the liver via two phases of reactions involving various groups of enzymes that belong to a family of cytochrome P450 in the liver cell cytoplasm.

Phase I is the conversion of functional groups such as dehydrogenation/hydrogenation, oxidation, hydrolysis (esterase), reduction and mono-oxygenation. The purpose of this phase is to reduce toxicity of each drug. Phase II is the process of derivitisation of functional groups in order to produce water soluble metabolites to be excreted through the kidneys. These are glucuronidation, sulphation, acetylation, Glutathione (GSH-Conjugation) and

Methylation. The metabolites produced from the two phases are less active than the parent drug or they may even be inactive. However, some may have enhanced activity or toxic effects, including mutagenesis, teratogenesis, and carcinogenesis, thus they need to be excreted through the kidneys efficiently.

In the context of opiates and opioids, only Morphine and its related compounds such as Hydromorphone and Oxo-morphone) go through the phase II directly via the enzyme uridine diphosphate glucuronyl transferrase 2B7 and its glucuronide conjugates are excreted in the urine. The Codeine, Hydrocodone, Oxycodone, Methadone, on the other hand have to go through the phase I conversion using cytochrome P450 series of iso-enzymes (Smith, 2009) and from there on, directly excreted in the urine. The same applies to Tramadol (narcotic like pain killer) and Fentanyl (synthetic opiate and tranquilizer). Certain CYP enzymes are shared amongst the opiates, Tramadol and Fentanyl (CYP2D6, CYP3A4 are shared by more than one drug) (Smith, 2009).

The shared metabolic pathways lead to a longer half-life for each of the drugs with a synergistic effect leading to a longer lasting euphoria (along with analgesia). Moreover, the rate of conversion and conjugation into water soluble metabolites would also be slower (as sharing the pathway), which lead to a reduced clearance from the body (Meyer, 1996)

Cannabis and tetra-hydro cannabis (THC)

These are the major active compound of Marijuana leaves which are used to wrap the Nyaope mixture; are also metabolised by the microsomal hydroxylation and oxidation pathway of the CYP450 isoenzyme complex as shown

in the figure 1. As Cannabis shares the metabolic pathway with most opiates and opioids via cytochrome enzymes CYP2D6 and 3D4, this causes sluggish renal excretion and increased blood levels of both groups which can result in a higher level of euphoria and a more severe addictive effect. The higher blood levels result in the tolerance to the effects of both drugs, making the user require another dose in a shorter time period (Maurer, Saucer, & Theobald, 2006).

Benzodiazepines

These are also found in Nyaope and they get metabolized in the liver through the CYP450 iso-enzyme complex, many of which are shared by the opiates and cannabinoids, and all metabolites of Benzodiazepines go through the final glucuronidation pathway in the liver before excreted by the kidneys. Due to extensive sharing of CYP metabolic enzymes between Benzodiazepines, opiates, opioids and cannabis, the CNS suppressant effects of each potentiates that of the others; may lead to severe drowsiness in the users (Oshiro, 2013).

Phenobarbitals

This has also been found in some Nyaope mixtures and if the users consume

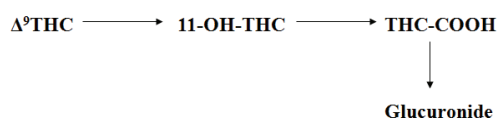


Figure 1. Metabolic route of Δ^9 -tetrahydrocannabinol (Δ^9 _THC), its primary active metabolite 11-hydroxy- Δ^9 -tetrahydrocannabinol (11-OH-THC) and the primary inactive metabolite, 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol (THCCOOH) (Sharma, 2012; Maurer, Saucer, & Theobald, 2006)

alcohol at the same time as smoking Nyaope, both can stimulate most of the P450 enzymes and enhance the metabolism of aforementioned drugs in Nyaope. This can lead to reduced plasma levels and increased tolerance, for example to Benzodiazepines (Meyer, 1996).

Amphetamine and methyl-amphetamine (CNS stimulants)

They constitute as major component of Nyaope and also get metabolized by the demethylation pathway of the CYP450 (2D6, 1A2, 2B6, 3A4) iso-enzymes, thus sharing with most of the opiates (Maurer, Kraemer, Springer, & Staack, 2004).

Other minor constituents

Amongst the minor constituents, caffeine and acetaminophen (paracetamol) as well as Dextromethorphan, and Lidocaine (local anaesthetics) have been found in the Nyaope mixture and they are metabolized by the CYP3A4 AND 1A2 enzymes (Meyer, 1996).

Drug Synergies between the major drug groups:

This means drugs with similar actions and when they are taken together, they potentiate each other's action and resultant effect is exponential. When opiate and Opioids are combined, based on the shared metabolic pathways of opiates mediated by cytochrome P450 liver enzymes, they inhibit the metabolism of each other, thus leading to longer plasma half-life and higher intensity of euphoria and addiction (Dean, 2006). Synergy between opiates and cannabis was found in animal studies where cannabis up-regulates the opiate receptor proteins in the brain. This evidence provided the basis of better strategies in pain management

of cancer patients (Cichewicz, 2004; Chimalakonda, Seely, Bratton, Brents, Moran, Endres, & Moran, 2012). Combination of Benzodiazepines and Phenobarbitone was also synergistic as both are in the sedative group that suppress CNS and when taken together, this action is profound as they synergise each other. They cause severe drowsiness and lack of orientation in time, place and person. During withdrawal, restlessness, sleep disturbance, irritability, increased tension and anxiety, panic attacks, hand tremor, sweating, difficulty in concentration, dry wrenching and nausea, some weight loss, palpitations, and headache are common (National Institute on Drug Abuse, 2016).

The synergy also manifests in the adverse effects of these combined drugs. For example, the gastro-intestinal symptoms are much more severe and sometimes unbearable when opiates such as cocaine, morphine and heroin are added with meth-amphetamine. There have been reports of life threatening abdominal complications that require surgery such as perforations due to mesenteric artery ischemia, reported by Tiwari, Moghal, and Meleagrow (2006) due to combination of opiates such as cocaine and heroin abuse. Severe chest pain due to ischemia of coronary vessels was also reported in another study by Burrows, Hagardorn, Harlan, Wallen, & Ferslew (2003) presented a case of a fatal drug interaction caused by ingestion of oxycodone and clonazepam. Oxycodone is an opium alkaloid used in long-term pain management therapy and Clonazepam is a benzodiazepine used for the treatment of seizures and panic disorders. The post-mortem shows pathologies consistent with severe central nervous system (CNS) and respiratory depression produced by

high concentrations of clonazepam and oxycodone including collapsed lungs, aspirated mucus, and heart failure.

When looking at the combination of CNS stimulants and suppressants, although it can be assumed that such combination would cancel each other's effect, paradoxical effect of synergy was reported (Wise, 1996). Wise claimed that there is a summative effect of brain reward (natural satisfaction as in food, sexual activity or change in chemical balance) of median forebrain bundle fibres in the human brain when they are exposed to the mixture of opiates (codeine, morphine, heroin) which are CNS suppressants and the CNS stimulants such as amphetamines, caffeine, nicotine, cannabis and phencyclidine. The reason behind this is because they share the site of stimulation in the brain through common mechanisms. The balance of these mixed effects is an enhanced stimulation in a shorter duration. This concept could be applicable in the case of Nyaope and also possible that since the amount of each drug is very small in the Nyaope mixture, the duration of stimulation is rather short but the height of euphoria causes stronger addiction.

In poly-drug use, the end result may lead to four possible outcomes such as null (cancelling effect), overlapping and addition (synergistic effect) and antagonistic effects (United States Maine County Law Department, 2010). For example, when central nervous system stimulants are combined (such as those found in Nyaope- Amphetamine, Meth-amphetamine, Cathine-beta hydroxyl amphetamine, Pipradrol, and Fenelthylline), they would lead to intense euphoria followed by severe side effects. Pupil size may be normal due to a cancellation of the constriction effect of narcotics

(opiates) and dilatation effect of stimulants and Cannabis. A lack of the pupil convergence effect however, can still be seen in the mixture of CNS suppressants and stimulant because the latter did not have any effect on it. A reaction to light would still be slow due to most of the drugs in the Nyaope mixture having this effect except Cannabis and anaesthetics. The pulse rate will depend on the proportion of Opiates, Opioids, Benzodiazepines, Phenobarbitone versus Amphetamine and Cannabis in the mixture the user has taken. The same goes for the blood pressure. Body temperature would be higher so long as there are CNS stimulant groups in the mixture, and the muscle tone (flaccid or rigid) would also depend on the proportion of suppressants and stimulants, although Cannabis has no effect on muscle tone. The drowsiness from Nyaope mainly comes from the combination of opiates, opioids and benzodiazepines as additive effect.

Combining Anti-retro viral therapy (ART) and drugs of abuse:

This was also seen in a few Nyaope mixture and although the rationale behind the mixing is not clear, some users during the interview, mentioned that the drugs help with the headache and insomnia caused by the ART (Mokwena & Huma, 2014). In the report of Thomas and Velaphi (2014) a combination of anti-retro viral (ARV) compounds and drugs of abuse such as Morphine and Nicotine enhances the CYP3A4 and MDR1 (multi-drug resistance protein) expression in vitro. Altered functions of efflux transporters within liver cells and CYPs in response to ARV and drugs of abuse may result in altered drug absorption and metabolism of both groups. Complexity underlying the relationship between efflux transporters and

CYP makes it difficult to predict the outcome of ARV therapy, particularly when HIV patients taking drugs of abuse do not adhere to this. HIV positive pregnant women on ARV medications and indulging in drugs of abuse, may develop a higher viral load due to such interactions, and lead to increase in mother to child transmission of HIV (Pal, Kwatra, Minocha, Paturi, Budda, & Miltra, 2011). Thomas and Velaphi (2014) reported two cases of neonatal abstinence syndrome and low birth weight of babies born to mothers who are on ARVs and known to be addicted to Nyaope in South Africa.

Combining antihistamines (cough syrup) in the Nyaope mixture:

The Dexamethorphen can be purchased as over the counter cough medicine and when co-used with opiates; it enhances the binding of opiates and opioids to their brain receptors potentiating the euphoria, but also contributes to the severity of combined drowsiness (Sandor, 2000)

DISCUSSION

It is not clear why the Nyaope mixture is formulated in this particular way. However, it can be postulated that it is based on the user's experience of synergistic effects, but other constituents such as acetaminophen and caffeine could be to avoid the side effect of headache. The fact that some samples contain Methadone is quite alarming as it is not known how chronic use of this drug would influence the Methadone treatment for Heroin in the rehabilitation (Braude & Ginzburg, 1986). Another author suggested that the rationale of combining CNS depressants and stimulants seems to lie with the

purpose of cancelling out each group's side effects as the former may lead to parasympathetic over activity and the latter, sympathetic counterpart (Armstrong & Cozza, 2003). Other minor components also seem to serve a specific purpose on their own, for example, plasticiser may enhance the stability of active ingredient powders in the mixture of ground cement or soil and it also accelerates the release of drugs from the matrix into the smoke upon burning. Plasticisers have been successfully used in the development of Transdermal drug administration such as skin patches for analgesics (Güngör & Erdal, 2011). The Local Anaesthetics (Durocaine/Lidocaine) is mildly euphoric and addictive (McLeod, 2015), but the rationale behind adding the antibiotics is not clear. In cases of Nyaope users who are already on ART, the rationale of mixing may be to curb the undesirable side effects of ARV such as headaches, insomnia or nausea. However, in cases where user is not HIV positive, the reason of adding it is not known. Interviews with the users showed that they were not aware that the mixture contained ARV.

The constituents were found to be variable from one area to another. This may be determined by the availability of raw material and also the demand pattern from the regular users. Some of the constituents such as local anaesthetics and medication for induction in general anaesthesia are only available at the hospital pharmacy, and drugs such as antibiotics and antiviral medication would need a prescription, implying that some dealers may have connections to these sources and that the operation of the Nyaope dealerships likely extends beyond the townships.

From the observations of Nyaope users at the Rehabilitation centres by the public

health practitioners (Mokwena & Huma 2014) the main presentation features are severe chest pain, abdominal cramps (a feeling of explosions in the stomach), tremendous drowsiness, vomiting and sometimes diarrhoea. On a physical level, small pupils and high blood pressure with tachycardia is usually seen. Moreover, poor personal hygiene, signs of malnutrition, dry skin and ulcers and marks due to old scars from obsessively scratching the skin (methyl amphetamine), thin and dehydrated face, burnt marks around the nostrils and mouth from combustion of certain drugs. There is also progressive weight loss from failure to eat and drink. Also reported are the feeling of irritability, insomnia, involuntary jaw clenching and tooth grinding.

In terms of treatment options for the withdrawal symptoms, it is mainly supportive and specific medication for substituting poly-drug use or the mixture is not available. A recommended treatment for chronic Heroin use is by substituting it with Methadone (United States National Institute of Health (On Drug of Abuse) Annual report, 2012), but this requires admission to a clinic for observation of treatment initially and followed by prescribing a maintenance dose of Methadone for a longer term (3-4 years) (Centre for Disease Control (CDC), 2002). The reason for observation is to ensure abstinence from Heroin and other drugs during therapy. The fact that the Nyaope mixture also contains Methadone defeats the purpose of Methadone based withdrawal treatment program as how a Methadone treatment would affect the other constituents in the Nyaope mixture has not been studied pharmacologically. Buprenorphine and Naltrexone are the other antidotes for opiates and they act

by antagonizing the opiate receptors, but due to the cannabis in Nyaope that increases the opiate receptors in brain, and these antidotes would not be as effective as expected (Cichewicz, 2004).

CONCLUSION

It is apparent from the literature review that the major drugs of abuse contained in Nyaope share the metabolic pathways leading to longer lasting plasma levels and synergistic effects of euphoria, but the trade-off is the tolerance and aggravation of side effects constituting the unique withdrawal symptoms. Treatment programs thus far are restricted to psycho-social therapy for behavioural change, and symptomatic treatment for withdrawal as specific medication for rehabilitation of Nyaope is still a complex phenomenon due to the mixture of various types of drugs. Understanding how metabolic pathways and drug interactions impact the clinical presentations in the users is thus important for the clinicians working in the withdrawal clinics and rehabilitation centres.

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