ACTA SCIENTIFIC NUTRITIONAL HEALTH

Volume 3 Issue 2 February 2019

Research Article

Codeine and its Histopathological Effect on Brain of Albino Rats: An Experimental Study

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Received: January 08, 2018; **Published:** January 22, 2019

Abstract

Codeine is a centrally acting synthetic analgesic agent with opioid activity. Codeine is used to treat moderate to severe pain. The consumption of codeine has lately attracted attention because of its strong reciprocal connections with psychological changes in addicts. This study was designed to demonstrate the histopathological changes in rat Brain tissues due to intake high doses of Codeine. Twenty adult rats (aged 2 -3 months) weighing 180-210gm were classified into four groups; group V (control group), group I (4 rats received 5mg/kg/6hrs of Codeine orally for 5 weeks), group II (4 Rats received 10mg/kg/6hrs of Codeine orally for 5 weeks), group III (4 Rats received 15mg/kg/6hrs of Codeine orally for 5 weeks), group IV (4 Rats received 20mg/kg/6hrs of Codeine orally for 5 weeks). All animals were anaesthetized by ether inhalation and perfused by normal saline. The brains were extracted from the skulls. For light microscopy, the brains of 4 animals in each group were processed for paraffin sections and stained using Hematoxylin and Eosin stain. Morphometric and Histological examination of Brain tissues specimens were performed. The results of this study demonstrated histological changes in brain tissues in group II compared to group I with increased pathological changes. It could be concluded that administration of Codeine have histological abnormalities on brain tissues associated with oxidative stress in these organs. Also, there is increased apoptosis. These findings may provide a possible explanation for psychological changes associated with Codeine abuse.

Keywords: Codeine; Brain; Histopathological; Albino Rats

Introduction

The history of the use of drugs or therapeutic agents dates back to that of medical practice itself. Drugs which are made up of a number of chemical component or compounds for therapeutic purposes may in some cases become toxic to the patient. The reason could be attributed to the fact that drug is a substance that brings about a change in biological function through its chemical actions [1].

Little is known about the extent of the histopathological consequence of misuse of opioid analgesic medications in Nigeria and Africa. Prescribed opioid analgesics are dispensed legally to patients for treatment of symptoms such as pain, cough and diarrhea, and are also widely available and accessible to the public in over the counter preparations. Increased purchases of over-the-counter analgesics without medical consultation have resulted in increased use of potentially habit-forming substances [2].

One such opioid analgesic medication which is of public health concern is the common weak opioid, dihydrocodeine which is widely used for its analgesic, antitussive and anti-diarrheal properties [3,4]. Dihydrocodeine is believed to be the "least addictive and safest" of all of the opiate drugs prescribed today [5]. This accounts for its being the most widely used drug within this category of analgesics. It should be remembered that being the least addictive and safest doesn't mean that Codeine is not addictive or safe.

The name codeine is derived from the Greek word kodeia (κώδεια) for 'poppy head' and it is found naturally in the poppy plant '*Papaver somniferum var. album*'. Codeine is a phenanthrene derivative extracted from opium or produced synthetically by the methylation of morphine.

Globally, the demand for codeine remains high and has risen by approximately 27% over the last decade [6]. Recent INCB figures demonstrate that global consumption reached an all-time high in 2011 at 269 tonnes. Both exports and manufacture of codeine have also seen a rising trend. In 2011, figures show that the UK was the highest codeine manufacturer globally representing 22%, followed by France (21%), US (17%) and Australia (8%). Over the counter sales of codeine containing medications is not easy to determine.

Sales of over the counter medicines information is protected because it is commercially sensitive and qualifies exemptions where information is a trade secret and where disclosure would likely prejudice the commercial interests of any person or public authority holding it. Over the counter sales of products containing codeine generally must be supervised by a pharmacist [7]. There is a standard scheduling of codeine across the EU, Australia, Canada, United States of America, Asia and South Africa.

Codeine is widely used in healthcare. The main therapeutic indications for codeine are the relief of mild to moderate pain and cough suppression. It is also used to a lesser degree as an anti-diarrhea agent. Like all drugs, codeine, is not free of problems [4]. It is however generally viewed as a safe and effective analgesic, despite calls to withdraw it from the market [4,8]. The effectiveness and role of codeine in treatment of minor and moderate pain is debatable.

The World Health Organizationhas placed Dihydrocodeine on 'step2' of its pain ladder, and it is commonly used in the management of mild to moderate pain in adults (often dental or postpartum) and under strict monitoring in children [7,9,10]. Some authorities have suggested omitting 'step 2' due to the potential 14 dependent properties and side effects of dihydrocodeine, and guidelines generally do not recommend codeine for management of pain, due to limited evidence of its effectiveness, variations in metabolism and availability of more predictable opioids. A meta-analysis of six studies by Derry., *et al*. [3], demonstrated combined ibuprofen (400mg) and codeine (25.6 to 60mg) has good analgesic efficiency, but underscored the lack of data relating to low dose codeine(<10mg), with limited data available on medium dose (10-20mg), and most relating to high dose (>20mg, 25.6 to 60mg). In general, codeine is thought to be effective in the treatment of non-cancer pain over a short period of time (less than 6 months). Long-term treatment with codeine cannot be supported as the evidence for its effectiveness is variable and the risk of misuse and abuse is significantly increased (Trescot., *et al.* 2008). Codeine is available in over the counter combination preparations with caffeine, paracetamol or ibuprofen. However, one of the main reasons for selling over the counter products as combined preparations is to decrease their addictive and abuse potential.

However, misuse of combination products particularly ibuprofen is associated with gastrointestinal hemorrhage, nephro-toxicity, hypocalcaemia and acute hemorrhagic necrotizing pancreatitis [11-24]. Codeine appears more clinically useful when combined with paracetamol [3,25-27], suggested that codeine-paracetamol combined preparations should be the treatment of choice for mild to moderate pain (for example headache, post-operative, osteoarticular and post traumatic) rather than non-steroidal anti-inflammatory drugs. Baratta., *et al*. [28], reported limited evidence for single dose oral ibuprofen plus codeine being more effective for postoperative pain than either drug in isolation. A meta-analysis of opioids for osteoarthritis of the knee or hip reported that modest benefits of codeine were outweighed by adverse consequences [29]. Equally given the low dose dihydrocodeine used in non-prescription medicines, it may be the case that non opioid analgesics perform better [30]. Moreover, ibuprofen (400mg) was shown to be statistically superior to dihydrocodeine (30mg, or 60mg) for relief of pain [31].

Dihydrocodeine (methyl morphine) is a strong mono acidic base and laevorotatory. It effloresces slowly in dry air and is affected by light. The chemical name of codeine phosphate is 7,8-didehydro-4,5alpha-epoxy-3-methoxy-17-methylmorphinan-6alpha-olphosphate (1:1) (salt) hemihydrate and has the empirical formula of $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1/2H_2O$. Codeine phosphate contains not less than 98.5 percent and not more than 101.0 percent of $C_{18}H_{21}NO_3$, H_3PO_4 calculated on the dried basis. Codeine molecular weight is 406.4. Each soluble tablet contains 30 mg (0.074 mmol) or 60 mg (0.15 mmol) of codeine phosphate. These tablets also contain lactose and sucrose. Soluble tablets of codeine phosphate are freely soluble in water.

Codeine is a short acting weak to mid-range opiate that has a low affinity and low intrinsic activity at the opioid receptors [26]. It is effectively a pro-drug meaning that the body must metabolize it to active metabolites before it becomes effective as a painkiller. The major metabolite is codeine-6- glucoronide, but most of the analgesic action is due to the production of morphine in the liver by the enzyme Cytochrome P450 2D6. The metabolism is by 0- and N- demethylation.

The entorhinal cortex (EC) (ento = interior, rhino = nose, entorhinal = interior to the rhinal sulcus) is part of the medial temporal lobe or hippocampal memory system and constitutes the major gateway between the hippocampal formation and the neocortex. The entorhinal cortex has initially attracted attention because of its strong reciprocal connections with the hippocampal formation and its involvement in certain brain disorders. It is divided into medial and lateral regions. Neurons in the entorhinal cortex are grouped into different layers that are characterized by a dominant cell type. Six layers are commonly distinguished, of which layers I and IV (lamina dissecans) are relatively free of neurons. The principal neurons of the entorhinal cortex, i.e., the neurons that are among the main recipients of incoming axons and constitute the major source of entorhinal output to a variety of cortical and subcortical structures are generally pyramidal cells or modified versions, the socalled stellate cells. Severe alteration of the entorhinal cortex is associated with several disorders of the human brain, importantly Alzheimer's disease, temporal lobe epilepsy and schizophrenia. Entorhinal atrophy is associated with mild memory loss as seen in individuals with mild cognitive impairment. Temporal lobe epilepsy is associated with marked degeneration in layer III of entorhinal cortex. So, this study aimed to assess the deleterious effects of Codeine on the entorhinal cortex of the adult male albino rats using histological studies.

Oxidative stress may arise as an imbalance between reactive oxygen species (ROS) production of and the ability to neutralize them via antioxidant enzymatic and/or non-enzymatic activity. Large amounts of reactive intermediates lead to cell component damage and production of secondary toxic compounds e.g., reactive aldehydes and ketones.

Apoptosis or programmed cell death which is an active process of normal cell death during development also, occurs as a result of the cytotoxic effect of various neurotoxins. Previous *In vitro* studies indicated that exposure to opioid receptor agonists increased their liability to death by apoptotic mechanisms. In addition, other studies have been revealed that chronic morphine administration in rats is associated with significant changes in the principal proteins involved in the apoptosis signaling which collectively leads to induction of apoptosis. This study links use of codeine on brain with its effect histopathologically on the brain. This study was performed to demonstrate the histopathological changes in rat cerebral cortex due to chronic usage of codeine.

Unless there is urgent intervention, experts have warned that Nigeria may be building a nation of drug addicts. This is not unconnected with latest reports which show that 3 million bottles of codeine are consumed daily in Kano and Jigawa States. Even the National Agency for Food and Drug Administration of Nigeria, NAFDAC, on 18th December, expressed worry over uncontrolled use of codeine containing cough syrups across the country. There is no family now that is not affected. Our children are at risk as much as our husbands, wives and other relatives. Codeine containing syrups are not supposed to be freely sold, they are not Over-the-Counter drugs but somehow, they get into the hands of people through the pharmacies or Patent medicine dealers. (NAFDAC; 2018). It was reported that in 2015 alone, over 2,205 people were arrested in North-West geo-political zone by the National Drug Law Enforcement Agency, NDLEA, over drug-related abuses. Benin, which borders Nigeria's west, is the second largest destination for Indian Tramadol globally. Some of the worst affected countries in West Africa are yet to make significant progress in tackling the opioid abuse. However, in the last decade, the continent has seen a significant rise in the non-medical use of codeine, which produces similar effects to the "high" caused by morphine. Codeine is not internationally regulated by the International Narcotics Control Board in obedience to the World Health Organization's wishes.

This project aims to take a view of the codeine saga as a histopathologist. To ascertain if there is a histopathological damage to the brain tissue which would have resulted in behavioral changes in addicts. The present study was designed to assess the deleterious effects of Codeine on the (brain tissue) entorhinal cortex of the adult male albino rats. Since the clinical adverse effect of codeine may have some covert serious impact on the cell of the brain tissue.

Materials and Methods

This chapter presents details of the research design, location of study, sample size, histological technique. Standard histological methods and materials were used in this research work.

Drugs

Dihydrocodeine, 30 mg capsules, was obtained from Digital Pharmaceutical, Enugu. Dihydrocodeine is an odorless, white to off-white crystalline powder that is readily soluble in both water and ethanol.

Design and Conduct of the Experiment

The study was carried out on 20 adult Albino rats. These animals were housed in the Animal House of Department of Anatomy,

University of Nigeria in a stainless steel urine cages containing bedding of fine wood which was changed twice weekly. They were divided according to their average, body weight into 5 (five) groups of four mices per group. The animal were acclimatized for 2 weeks at the Animal House of Department of Anatomy, University of Nigeria, Enugu where the experiment was done. They were maintained under light dark cycle (12/12) hours, at a (25 ± 5) C. All rats were fed ad libitum with Standard Top Feed® and tap water. This experiment was complied with the known guidelines of animal ethics committee, which were established in accordance with the internationally accepted principles for laboratory animal use and care.

Location of Study

The study was carried out in the animal house of Department of Anatomy, University of Nigeria in a stainless steel urine cages.

Enugu state is an inland state in the south-eastern Nigeria. Its capital is Enugu. It was created in 1991 from part of the old Anambra State. The principal cities in the state are Enugu, Ngwo, Agbani, and Awgu. It shares border with Imo and Abia states to the south, Ebonyi state to the East, Benue state to the North-east, Kogi states to the North-west and Anambra state to the west. Lying partly within the semi-tropical rainforest belt of the south, the state spreads towards the north through a land area of approximately 87.271km^2.

Its physical features change gradually from tropical rainforest to open woodland and then to savannah. Apart from a chain of low hills, running through Abakiliki, Ebonyi state in the east to Nsukka in the North-West and southwards through Enugu and Agwu, the rest of the state is made up of low lands separated by numerous streams and roulettes, the major ones of which are the Adada River and the Oji River. Enugu has good soil and climate, sitting at about 223 meters above sea level and the soil is well drained. The mean temperature in Enugu state is in the hottest month of February which is about 36.2^{o}C (97.16F) While the lowest temperature occurs in the month of November reaching about 20.3^{o}C (68.58F). The amount of rainfall measured in this state varies between 0.16cm^3 in February and about 35.7cm^3 in July.

Animal Population

The animals used were Albino rats. A total of 20 male rats were used with weight ranging within 180 - 200g. They were 4-6 weeks old. They were divided into 5 groups. Each group made of 4 Albino Rats.

Materials and Equipment

Stainless steel cages, Feeders and Mice Feeds, Marking tape and marker, Glass slides (frosted), Cannula and syringe, Injection water pack, Measuring cylinder, Leica Histokinette, Immersion Oil, Hematoxylin stain, Epson Stain, Light Microscope.

Experimental protocol

The animals were all weighed before commencement of drug administration and at the end of the experiment. The animal aged 2-3 months were divided into 5 cages (A, B, C, D and E) with each cage containing 4 rats, not sex matched, but according to their weight as follow 181.5g, 190.1g, 193.8g, 198.9g, 200.3g respectively. The animals were feed with Standard Top Feed®, tap water and cage one (A) to four (D) received oral administration of Dihydrocodeine daily for 35 days. Cage five (E) was the control group and receive no drug administration.

The drug was obtained from a standard pharmaceutical store and the tablet was dissolved to get the appropriate concentration using commercially obtained injection water. The drug was administrated orally using oral cannula made from 1ml plastic syringes without needle.

Method

For this study, the drug was administrated in the prepared solution.

Cages	Number (rats)	Average Weight (g)	Dosage (mg/kg/6hrs)	Number of Days of Administration
A	5	181.5	5	35
B	5	190.1	10	35
C	5	193.8	15	35
D	5	198.9	20	35
E	5	200.3	----	-

Table 1: Oral Administration of Dihydrocodeine into Albino Rats.

Average weight of all the Rats; 192.92g

Therapeutic Dose; 1mg/kg/6hrs

Each of the animals in cage A to D was picked at a time with a clean napkin and appropriated volume of the drug solution was administered orally using 1ml plastic syringes without needle to ensure complete delivery of the drug orally to the gastrointestinal tract of the animal.

This was done daily for 35 days. The animals was weighed, anaesthetized with chloroform on 37th day and scarified at the animal house at the end of the period of drug administration. Intracardiac perfusion was done using 2.5% glutaldehyde at P^H 7.4 for partial fixation of specimens. Craniotomy was performed to dissect out the intact brains for histological studies. They were observed grossly and thereafter processed for light microscopically examination.

Processing samples for histology

The brain tissue was processed, sectioned and stained. Observation was made using the microscope. The tissue was prepared using Leica automated tissue processor, Histokinette. The tissue processor prepares tissue samples for sectioning and microscopic examination in the diagnostic laboratory. Microscopic analysis of cells and tissues requires the preparation of very thin, high quality sections (slices) mounted on glass slides and appropriately stained to demonstrate normal and abnormal structures. The ATPM works by following through an already established processing step. Tissues to be processed were cut into small pieces to ensure the tissue fits into the tissue cassettes. Smaller tissues (2-4um) are processed faster than the whole tissue or organ. These tissue cassettes were packed into the oscillating tissue basket prior to fixation. The tissue was processed, fixed, dehydrated, cleared in xylene, embedded, sections of 5 microns thickness were cut with rotary microtome and stained with Haematoxylin and Eosin.

Microscopy and photomicrography

The sections were examined using swift binocular microscope system with in-built light system. Photographs of the sections were obtained using 35mm colored films with an Olympus photomicroscope.

Results

Physical observation made before scarified is that animals of higher dose were sluggish and restless while the cage E that served as the control were very active and looks healthy. There was a significant weight look of the animals. But there is no weight loss in the cage (E).

Grossly, the brain of the animals showed a color variation. In addition, there were some physical features of damage to the brain expressed by the animal.

Examination of H&E stained sections of control group showed that the cerebral cortex showed groups of nerve cells arranged in well-organized six layers, outer molecular layer covered with pia mater, outer granular layer, outer pyramidal layer, inner granular layer, and inner pyramidal and polymorphic layers. The pyramidal cells showed open face nuclei, basophilic cytoplasm and long apical dendrite. The granular cells appeared rounded in shape and showed large rounded vesicular nuclei with prominent nucleoli. Glial cells appeared smaller in size with small deeply stained nuclei. The ground substance between the nerve cells is normally occupied with homogenous eosinophilic background (neutropil) formed of neuronal and glial cell processes.

Plate 1: Photomicrographs of a coronal section in brain tissue of control group showed a delicate layer of pia matter (arrow) and six layers of the motor cortex were demonstrated; outer molecular (I); external granular (II), external pyramidal (III); inner granular (IV); inner pyramidal (V); and the polymorphic layer (VI). Blood capillaries (notched arrows) were also observed (H&E × 100). Large pyramidal cells (arrows) with basophilic cytoplasm, large vesicular nucleus and long apical dendrite were observed. Granular cells (crossed arrows) with large rounded vesicular nuclei were detected. The glial cells (arrow heads) with small dense nuclei were also seen. Note, eosinophilic neuropil (asterisks) formed the background for the cells (H&E × 400).

Examination of H&E stained sections of codeine treated group showed marked disorganization of the cortical layers and hypercellularity as well as increased apoptotic cells. Additionally, extensive neutropil vacuolization and multinuclear giant cells were also seen. Almost all pyramidal cells appeared irregular in shape, darkly stained with pyknotic nuclei and surrounded by haloes others were shrunken and showed marked cytoplasmic vacuolization. Some pyramidal cells appeared with faintly stained cytoplasm and nuclei. Some regions of the neutropil showed dilated blood vessels, cellular infiltrate and red neurons (neurons with hypoxic changes).

Plate 2: Photomicrographs of a coronal section in the medial entorhinal area of control group. It shows neuronal cells organized in layers I, II, III, IV, V and VI [H&E]. Their nuclei (arrow) have prominent nucleoli (arrow heads) [H & E]. It shows dark neurons with hyperbasophilia (arrowheads), diffuse chromatolysis of nuclear chromatin and absence of nucleoli (crossed arrows), absence of nuclei (arrow), degenerative vacuolization (crosses) and intercellular edema (stars) in layers I and II [H&E]. Presence dark neurons with hyperbasophilia (arrow head), absence of nuclei (arrow) and intercellular edema (star) in layer III [H&E].

Plate 3: A photomicrograph of a section from the cerebral cortex of a rat of group A & B showing neuronal cell disorganization and hypercellularity as well as increased apoptotic cells (arrow), multinuclear giant cells (crossed arrow) extensive neuropil vacuolization (V) and inflammatory cell infiltrations (arrow head) (H&E × 400).

Plate 4: A photomicrograph of a section from the cerebral cortex of a rat of group C showing some irregular darkly stained pyramidal cells with pyknotic nuclei and surrounded by haloes (arrows) others are shrunken and shows marked cytoplasmic vacuolization (crossed arrow). Some pyramidal cells appear with faintly stained cytoplasm and nuclei (arrow head). Note the presence of dilated congested blood vessels with inflammatory cells in it (curved arrow) and the red neurons (short arrow) (H&E × 400).

Plate 5: A photomicrograph of a section from the frontal motor area of the cerebral cortex of a rat of group D showing normal pyramidal cells (arrow), granular cells (crossed arrow) and blood vessel (curved arrow). Some pyramidal cells are shrunken and surrounded by haloes (arrow head) (H&E × 400).

Cages	Dose mg/kg/6hrs	Average Weight before administration	Average weight after administration	Physical parameter
				Loss or gain
A	5	181.5	180.3	
B	10	190.1	184.4	
D	15	193.8	172.8	
C	20	198.9	170.4	
E	-	200.3	239.2	

Table 2: Result of effect of Codeine on Physical Parameters of Albino Rats.

Key: ------- = Normal features

⇩ = Marked decrease in weight

⇧ = Marked increase in weight

		Histological Scoring						
					BRAIN			
	Dosage (mg/kg/6hrs)		Inflammatory cell infiltration	Vacoulation	Inflammatory cell infiltration	Frank red blood cell	RED NEURONS	Multi Nuclei Giant cells
A	5	-	-	-	±	+	-	+
B	10	-	-	-	±	+	+	+
C	15	-	+	+	++	++	+	++
D	20	+	+	+	+++	+++	+	+++
E	-	-	-	-	-	-	-	-

Table 3: Result of Sub-acute toxicity of codeine on Albino rats for Days.

Key:

- = Normal feature
- ± = Intermediate feature
- \+ = Presence feature
- ++ = Marked presence of feature
- +++ = Large presence of feature

Discussion and Conclusion

The rate of abuse of drugs and other chemotherapeutics seems to be increasing daily. A lot of patients are placed on long-term administration of some clinically useful drugs such as Codeine which may have cellular adverse effects. This works was carryout to investigate and characterize the adverse effects of codeine.

The current study aimed to assess the deleterious effects of Codeine on the brain tissues of the adult male albino rats. From the study, apoptosis was proved in brain tissues of Codeine treated rats by light microscopic examination as there was marked cortical layers disorganization and hypercellularity as well as increased apoptotic cells. Additionally, extensive neutropil vacuolization and multinuclear giant cells were also seen.

Degenerated pyramidal cells appeared either darkly stained with pyknotic nuclei or with faintly stained cytoplasm and nuclei. Some pyramidal cells were shrunken and showed marked cytoplasmic vacuolization. This vacuolation could be attributed to the damaged cell organoid from exposure to free radicals. Some regions of the neuropil showed dilated blood vessels, cellular infiltrate and red neurons (neurons with hypoxic changes) which coincides with the results that observed by Mohamed [32]. They listed their histological finding of brain and revealed that pyramidal cells lost its

shape, perivascular space increased with hemorrhage, disrupted ependyma, and choroid plexus became hypertrophied. These results were also observed by another study done by Abou-El-Fatoh., *et al.* [33] as they found congestion of submeningeal blood vessels and neural degeneration following tramadol. Moreover, Liu., *et al.* [34] found that the apoptotic cells were present with cytoplasmic contraction, reduction in cell volume and nuclear condensation.

The apoptotic cells were detached from surrounding cells by Tunnel technique in addition to large amount of apoptotic signals were observed in the nucleus of neurons in the group utilizing opiate as they utilized morphine in their study. In group III, most of the histological findings were subsided as there was return of brain tissues towards normal morphology as evidenced by decreased cellularity and decreased perineuronal haloes as well as normal blood vessels. Multiple pyramidal cells and granular cells appeared normal; however, few pyramidal cells are shrunken and surrounded by haloes.

This indicates that the apoptosis activity as well as the oxidative stress damage of brain tissue mostly decreased in this group. These results are in agreement with Khodeary., *et al*. [35]. They stated that whereas rats examined after some peroid unlikely showed partial recovery (did not return back to normal control) but marked reduction in cellular damage was observed when compared to other treated groups [36].

In conclusion, this research work is suggestive that consumption and administration of codeine may induce have histological abnormalities on brain tissues. Finally, these findings may provide a possible explanation for the behavioral and psychological changes associated with codeine abuse.

Codeine abuse should be avoided due to its toxic effects. Further investigations are needed for information to unravel the danger of codeine on other body system. Also, the histological effects of codeine include serious harm which may remain insidious over years, as a result of long-term administration. This calls for attention to histology especially for the brain tissues in cases of abuse and long term administration. Also, many chronic chemical or morphological changes in the body do not manifest while taking normal doses for 20-30 years, thus the need to monitor and control these changes together with therapy.

Recommendations

It is recommended that:

1. Discouragement of prescription of marked out drugs by overzealous health practitioners without laboratory follow-up,
2. Drug consumption, distribution and production should be strictly controlled. The work done by national drug Law Enforcement Agency (NDLEA) is recommendable and should be holistically practiced to extricate the healthy addicts of this drug.
3. Development of drug research control/toxicology laboratories by the government where drugs will be studied and improved to reduce the adverse effect to the body cell should be embraced and encouraged.

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