Luis M. Llosa, MD

Brief Review of Oral Cocaine for the Treatment of Cocaine Dependence

History, Botany, Chemistry, Sources, Pharmacology, Toxicology, Toxicity, Substitution, Classification, Clinical Researches, Legal Status, References.

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New York, 2010

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- Juan Gutemberg-Editors EIRL
- New York, 2010

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Coca Médica, Anglo American Medical Tower, Psychiatry Service,
San Isidro, Lima, Perú

Dedicated to
my mother Rocío,
and Helen

INTRODUCTION

In 2008, 5.3 million Americans age 12 and older had abused cocaine in some form.

1.1 million had abused crack at least once in the year prior to being surveyed.

This revision is intended to learn about the psychophysiological effects of the uses of coca leaves and derivatives in the human organism, and to demonstrate the effects of oral cocaine in the treatment of cocaine dependence.

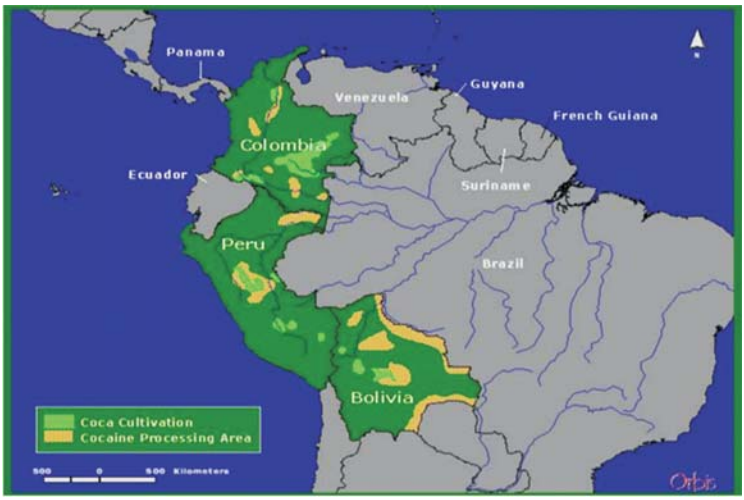
COCA PLANT: HISTORY AND BOTANICAL DATA

Native to South America.
First mentioned by Americo Vespucio in 1540 «plant chewed by the Indians with a white powder and only used by males» (Garcilaso de la Vega, 1609).
Archeological findings in Ancon, Peru, established that chewing coca was already a custom 5000 years ago (Patterson 1971).
Two different but related species of plants – Genus Erythroxylum known as Bolivian Coca and Genus Novogranatense known as Colombian Coca (Morris 1889).
There are four varieties of Erythroxylum Coca- incl. Lambran (has the highest cocaine content), Truxillense (has the highest content of fatty acids- used for its flavor) (Machado 1969).

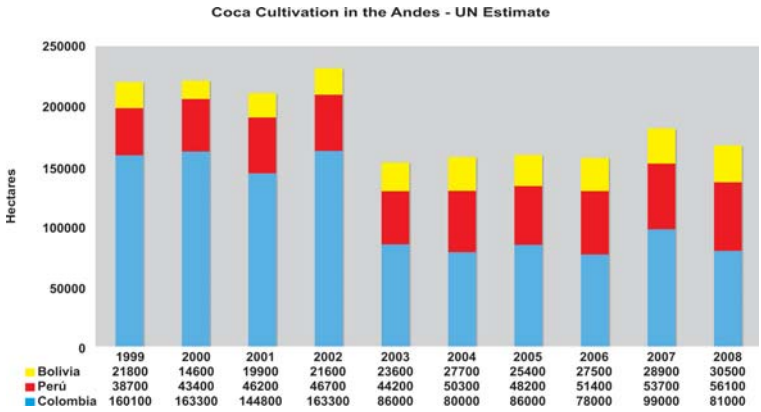
Garcilaso de la Vega, Inca (1609) Comentarios Reales. Biblioteca Ayacucho, Caracas (1976)
Morris D (1889) Coca, Kew Bulletin, 25: 1-13
Machado E (1969) El género Erythroxylum en el Perú, Las cocas silvestres y cultivadas del país. Ranmoidiana 5: 5-101
Patterson TC (1971) Central Perú: its population and economy, Archeology 24: 316-321

GEOGRAPHICAL DISTRIBUTION OF THE COCA PLANT

Today there are more than 100,000 hectares used for Coca cultivation. Today Colombia is the main producer of coca leaves, the vast majority used for narcotic traffic:
Colombia > Peru > Bolivia.
Between 10% and 20% is used for traditional purposes. The rest is used for illegal activities.
(**University of Southern Maine)**



COCAINE PRODUCTION IN THE ANDES



LEGAL REGULATIONS

Coca plant (coca leaves) an cocaine alkaloid have the same restrictions. Cocaine restrictions appeared 40-50 years after its discovery and extraction in 1860.

Act of the United Nations Conference in 1961, New York, prohibited the cultivation of new coca plantations and its eradication in 25 years (1989). Code of Federal Regulations state- «Coca leaves and any salt, compound, derivative, stereoisomers of cocaine, or preparation of coca leaves, and any salt, compound, stereoisomers of cocaine, derivative, or preparation thereof which is chemically equivalent or identical with any of these substances, but not including decocainized coca leaves or extractions of coca leaves which do not contain cocaine or ecgonine. In the US cocaine is a Schedule II substance (Karch 1998).

Currently coca leaf cultivation is only permitted in traditional and historical areas such as Cusco in Peru and Yungas in Bolivia (WHO/EB120/36, Dec 2006). In these countries many coca derivative products are licensed to be sold over the counter, and present historic bipolarity – praised and sacred plant to evil and illegal drug.

Karch SB (1998) Drug Abuse Handbook, SB Karch (ed) CRC Press

COCA LEAVES

Composition

Contains between 0.25% to 2.25% of alkaloids.

Fourteen alkaloids have been identified.

They also contain high doses of Calcium, Iron, Phosphorus, Thiamine , beta carotene, protein, fatty acids, and fiber (Collazos et al 1965; Martin 1970; Duke et al. 1975)

Coca Tea, popular beverage in Andean

Collazos C, Urquieta R, Alvistur E (1965) Nutrición y Coqueo, Revista del Viernes Médico, Vol XVI, N° 1, Lima

Martin RT (1970) The role of Coca in the History, Religion, and Medicine of South American Indians. Economic Botany, 24: 422-438

Duke J, Aulik D, Plowman T (1975) Nutritional value of Coca, Botanical Museum Leaflets, 24: 113-119

COCA LEAF: COCAINE

Cocaine (cocaine alkaloid, cocaine base) (ONU 1986)

- Is the name of one of the alkaloids found in coca leaves and makes up about 70% of all alkaloids in the leaf (depending on the type of plant).
- Chemical natural cocaine is also known as l-cocaine, beta cocaine or methylbenzoylecgonine.
- It is an alcoholic base related to atropine.
- Hydrolized to benzolecgonine when exposed to a very high pH > 10.
- Cocaine is hydrolyzed by the plasma and liver pseudocholinesterases.
- Its vitro half life is 60 minutes.
- Its main metabolites are benzoylecgonine and methylesterecgonine.

ONU ST/NAR/7 (1986) Métodos recomendados para el ensayo de la cocaína. NNUU División de Estupefacientes, Viena, New York

THE PLANT AND ITS USES

Natural

The oldest and most popular way to use the coca is by chewing or as an infusion of its leaves (Unánue 1794; Carter, Mamani 1978; Cáceres 1978; Cabieses 1985)

As they are chewed (chacchado) they are mixed with a substance called llipta (made out of seeds and other substances of alkaline pH) in order to extract the cocaine from the coca leaves (Carrol 1977) and increase intestinal absorption (Llosa, Chang 2007).

Infusions are made out of coca leaves (traditionally) or coca leaf tea bags (mate de coca). As an infusion in hot waters allows the release of cocaine.

The prevalence of coca leaf use is 90.1% in Bolivia, 5% to 20% in Peru, 5% in Ecuador and <0.1% in Colombia (Montoya, Chilcoat 1996).

Unánue H (1794) Disertaciones sobre el aspecto, cultivo, comercio y virtudes de la famosa planta del Perú nombrada coca, Mercurio Peruano 11: 205-257

Carroll E (1977) Coca: The Plant and its Use. In: Cocaine 1977, NIDA Research Monograph Series, 13: 35-45

Carter W, Mamani M (1978) Patrones de uso de la coca en Bolivia. En: La Coca Andina, 205-250, La Paz

Cáceres B (1978) La coca en el mundo andino, America Indígena, 38(4): 769-785

Cabieses F (1980) Aspectos etnológicos de la coca y de la cocaína, En: Cocaína 1980, Jerí (ed) , Lima.

Llosa T, Chang-Fung E (2007) Efficient Absorption of oral cocaine contained in coca poder: a new form of use oral cocaine in Andean regions, NIDA/CPDD 69th meeting, Quebec City, Canada, June 16-21

Montoya ID, Chilcoat HD (1996) Epidemiology of coca derivatives use in the Andean region: a tale of five countries, Substance use & Misuse, 31 (10): 1227-1240

COCA PLANT: INDUSTRIAL DERIVATIVES

Manufacturing products

In the mid to late 1800's there were many products made with coca leaves, but the most famous and popular were the Mariani wine and the Coca Cola soda (Mariani 1896). An analysis of coca wines in 1986 reports a range of 5 to 12 mg of cocaine per ounce. Mariani´s wine was recorded as 8 mg per ounce (The Druggists Circular 1886). The range for the popular wine was from 3 mg to 18 mg of cocaine in a single dose (Musto 1992). Mariani´s wine contained about 35 to 75mg of cocaine per bottle (Andrews, Solomon 1975)

In Britain a popular «medicated» drink called Hall's Wine contained 4mg of cocaine in 1 ½ glasses (Musto 1992).

The Druggists Circular and Chemical Gazette, 1886 Vol 30, p 32
Mariani A (1896) Coca and its therapeutic applications, 3ra ed, JN Jaros, New York
Andrews G, Solomon D (1975) The coca leaf and cocaine papers (Andrews & Solomon, eds), Harcourt Brace Jovanovich
Musto D (1992) Cocaine´s history, especially the American experience. Cocaine: scientific and social dimensions, Wiley, Chichester (Ciba Symposium 166) p 7-19

COLA COLA: the oldest and well known product of coca leaves

Coca Cola appeared in Atlanta, USA, in 1886. Pemberton (1986) and Candler (1889) were the promoters of this drink that is made today, although not containing cocaine that had its original formula. As Mariani wine was promoted as a tonic to improve mood, and after as refreshing soda (Andrews, Solomon 1975).
Coca Cola used fresh coca leaves until 1900 with reports of having up to 2.5 mg of cocaine per 100 ml glass. For a six ounce bottle this would be about 4.5 mg. Currently Coca Cola contains decocainized coca leaves as one of its natural flavors, plus caffeine (Musto 1992).

A coca extract is still used in some energy drinks and as a nutritional supplement (coca powder) in the Andean Countries.

Andrews G, Solomon D (1975) The coca leaf and cocaine papers (Andrews & Solomon, eds), Harcourt Brace Jovanovich

The oldest worldwide industrial coca product

TRADITIONAL USES OF COCA LEAVES

Typical Andean coca Chewer

Use of coca in the maning work

COCA INDUSTRIAL PRODUCTS USED FOR AGONIST THERAPY

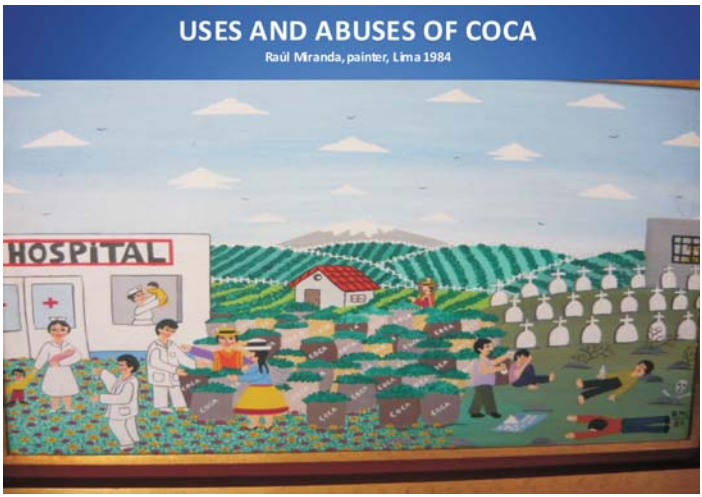
Cocaine alkaloid as coca powder in capsules (Perú)

Coca powder and capsules containing coca powder (Perú)

COCA DERIVATIVES FOR ADDICTIVE AND ILLEGAL USES

Coca Paste (pasta de coca, pasta, base, basuco)
Coca leaves macerated and mixed with toxic substances (sulfuric acid, cocaine sulfate, kerosene, gasoline and other impurities) smoked with tobacco or marijuana (Morales-Vaca 1984).
Contains about 50% of cocaine alkaloid.
One of the most toxic drugs found on the street.
Smoke produces by pyrolisis the metabolite called methylecgonidine (Novack, Salemink 1984).
Considered as double addiction cocaine/nicotine (Llosa, Henningfield 1993; Llosa 2009)
Not commonly found out of Andean regions.

Morales-Vaca (1984) A laboratory approach to the control of cocaine in Bolivia. Bull on Narcotics Vol XXXVI, N° 2, April-June
Novack Salemink (1984) A model experiment in the study of cocaine base smoking. Isolation of methyl 4-(3-pyridyl) butyrate from cocaine pyrolysate. Bulletin on Narcotics Vol XXXVI, 2, April-June
Llosa T, Henningfield J (1993) Analysis of coca paste cigarettes, Tobacco Control , An Internaztional Journal, 2 (4): 333
Llosa (2009) Smoking coca paste and crack-tobacco must be treated as double addiction, Substance Abuse, Vol 30 (1): 81



In Andean regions people is to accostumed use (chew) a mean of 30 gram to 50 gram (containing between 150 mg to 250 mg) of fresh coca leaves daily, mean six days a week during a year) mixed with a alkaline substance named lime/llipta/ toqra (Carroll 1977; Carter, Mamani 1978).

Carroll E (1977) Coca: The Plant and its Use. In: Cocaine 1977, NIDA Research Monograph Series, 13: 35-45
Carter W, Mamani M (1978) Patrones de uso de la coca en Bolivia. En: La Coca Andina, 205-250, La Paz

Cocaine Hydrochloride

Product of coca paste refined with hydrochloric acid (98% or better purity) (Karch 1998).

The most popular chemical presentation of cocaine used as an anesthetic or for illegal/addictive purposes.

As an anesthetic has been replaced by synthetic anesthetics with less potential for abuse (used in some ophthalmological procedures).

Found in the illegal market at 12% to 75% purity, mixed with sugar, amphetamine, anesthetics or caffeine.

About 1% of cocaine hydrochloride can survive heat combustion during smoking (Arif 1987).

Solubility in water is high which makes its absorption easy in water (ONU ST/NAR/7, 1986).

Arif A (1987) Adverse health consequences of cocaine abuse, Arif (ed) , World Health Organization, Geneva

Free basing

Cocaine hydrochloride is converted to its alkaloid by treatment with an alkali (ammonia) and a solvent (ether) which causes evaporation.

Has a lower vaporizing point than cocaine hydrochloride and thus less is lost when inhaled (Arif 1987).

Crack Cocaine

«Crack» is a solid form of freebased cocaine.

Called «crack» because it snaps and cracks when heated and smoked.

Differs from freebase only in the process to obtain cocaine by adding Sodium Bicarbonate (Baking Soda) and water to cocaine hydrochloride.

As with freebase, crack is smoked in a water pipe, which is usually made out of glass (Weiss, Mirin, Bartel 1994).

Weiss RD, Mirin SM, Bartel RL(1994) Cocaine (2° edition) RD Weiss, Mirin SM & Bartel RL (eds), American Psychiatry Press, Inc

NEUROBIOLOGY OF COCAINE

Cocaine binds differentially to the dopamine, serotonin, and nor epinephrine transport proteins and directly prevents the re-uptake of dopamine, serotonin, and norepinephrine into pre-synaptic neurons (Heikkila et al. 1975; Ritz et al. 1987; Volkow 2002). The euphoria or psychological effects are thought to be related to the inhibition of Serotonin and Dopamine reuptake. (Jenkins, Cone 1998). The intensity with which cocaine produces alterations in the dopaminergic circuitry is what has enabled this drug to prevail as one of the most addictive substances known to man (Hummel 2002). Also acts as a local anesthetic due to its ability to block Na+ channels in neurons. Physiological effects of this stimulation include tachycardia, vasoconstriction, mydriasis and hyperthermia. Central nervous system stimulation results in increased alertness, reduced appetite and increased energy.

THE REWARD SYSTEM

(The National Institute on Drug Abuse (NIDA) Teaching Guidelines (Positive Reinforcement)

The reward pathway is activated by a rewarding stimulus.

Natural rewards include food, water, and sex - each is required to maintain survival of our species.

Animals and people will continue to exhibit a behavior that is rewarding, and they will cease that behavior when the reward is no longer present.

Artificial rewards include drugs of abuse.

Although cocaine reaches all areas of the brain, it concentrates in some specific areas (mainly the reward pathway). It also concentrates highly in the caudate nucleus which can explain other effects such as increased stereotypic behaviors (pacing, nail-biting, scratching, etc).

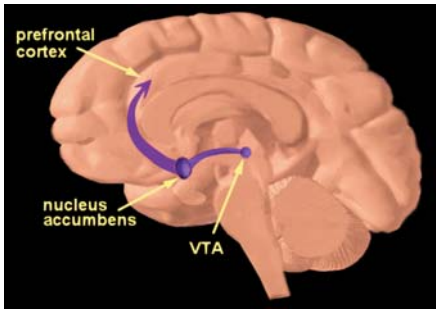
Heikkila RE, Orlansky H, Cohen G (1975) Studies on the distinction between uptake inhibition and release of (^{3}H)dopamine in rat brain tissue slices. Biochem Pharmacol 24: 847-852

Ritz MC, Lamb RJ, Goldberg SR, Kuhar MJ (1987) Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science 237:1219-1223

Volkow ND, Fowler JS, and Wang GJ (2002) Role of dopamine in drug reinforcement and addiction in humans: results from imaging studies. Behav Pharmacol 13: 355-366.

Hummel M, Unterwald EM (2002). D1 dopamine receptor: a putative neurochemical and behavioral link to cocaine action. *J Cell Physiol,* Apr;191(1):17-27

Jenkins A, Cone EJ (1998) Pharmacokinetcics: Drug absorption, distribution, and elimination, Chapter 3, 151-202. IN: Karch SB (1998) Drug Abuse Handbook, SB Karch (ed) CRC Press.



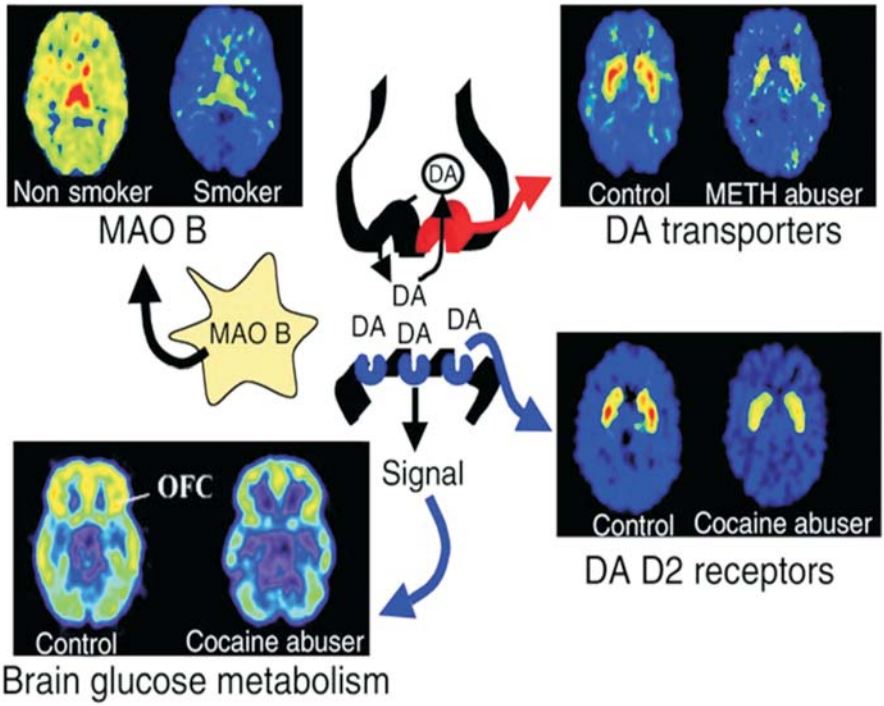
BRAIN IMAGENS

It has been demonstrated with cerebral PET Scan (SPECT) that cocaine consumers lower their number of D_2 receptors and that this is related to the reduction in frontal metabolism. SPECT also shows significant changes in glucose metabolism in the frontal cortical regions. The period of time it takes for the brain to recover its basal metabolism can easily take more than a year after sustained abstinence (Volkow et al 1991; Volkow 1997; Volkow et al 2003).

There are no studies with brain images in patients that ingest coca tea or coca powder for oral cocaine agonist therapy, nor in coca paste (cocaine plus nicotine) addicted patients under agonist therapy.

Volkow ND, Fowler JS, Wolf AP (1991) Changes in brain glucose metabolism in cocaine dependence and withdrawal. Am J. Psychiatry, 148: 621-626

Volkow ND (1997) The role of dopamine system in addiction. In: New understanding of drug addiction. Hospital Practice, Special report, April Volkow ND, Fowler JS, Wang G-J (2003) The addicted human brain: insights from imaging studies, J. Clin. Invest. 111(10): 1444-1451



PHARMACOLOGY OF ORAL COCAINE

The faster the drug is absorbed, the more intense the resulting high, but also the shorter the duration.

The duration of cocaine's euphoric effect depends upon the route of administration.

Cocaine is detected in plasma immediately after smoking or IV administration.

Cocaine is detected in plasma after 3-5 minutes when taken through nasal aspiration (snorting).

Cocaine is not detected in plasma until 15-30 minutes after oral administration.

The high from smoking or IV use of cocaine is immediate but lasts only 5 to 10 minutes.

The high from snorting cocaine takes longer to arrive but lasts 15-30 minutes.

Oral cocaine induces a pleasant and subtle sense of well-being that can hardly be described as a «high».

Bioavailability is 57% following snorting and ~70% following smoking.

The oral bioavailability of oral cocaine is 20% to 30% (Verebey, Gold, 1988).

Verebey K, Gold MS (1988) From Coca Leaves to Crack: the effects of dose and routes of administration in abuse liability, Psych Ann 18: 513-520

In Lima (sea level), Perú, thousand foreign tourists drink coca tea and eat coca powder products contained cocaine alkaloid. Coca products to oral and dermal use are sold legally over the counter.

ABSORPTION AND METABOLISM

After the digestive absorption of oral cocaine the concentrations in blood rise slowly in about 10 to 15 minutes. The slower and more sloped peak in blood levels is thought to be responsible for the apparent low rate of addiction of the oral route (Verebey, Gold, 1988).
The physiological and psychological effects of oral cocaine last twice as long as those when used by aspiration, three times as those used by IV route and five to ten times longer than those when smoked. This gives it many therapeutic advantages: a slow absorption avoiding its accumulation and toxicity, low blood concentrations, low but sensible physiological and psychological effects (Cone at al 1995).

Studies of the oral route of administration found that chewing powderer coca leaves containing between 17 and 48 mg of cocaine produce peak plasma concentrations of 11 to 149 ng/mL (N=6) at 0.4 to 2 h after administration (Holmstedt et al 1979). In another study, healthy male volunteers were administered cocaine hydrochloride (2 mg/kg) in gelatin capsules. Peak plasma concentrations of 104 to 424 ng/mL were achieved at 50 to 90 min (Wilkinson et al 1980).

When cocaine enters the digestive tract is mainly absorbed through the intestine (duodenum).
The cocaine alkaloid is released efficiently from the coca leaves in two ways: 1. in hot water (infusion), 2. mixed with an alkaline substance (Llosa, Chang-Fung 2007).

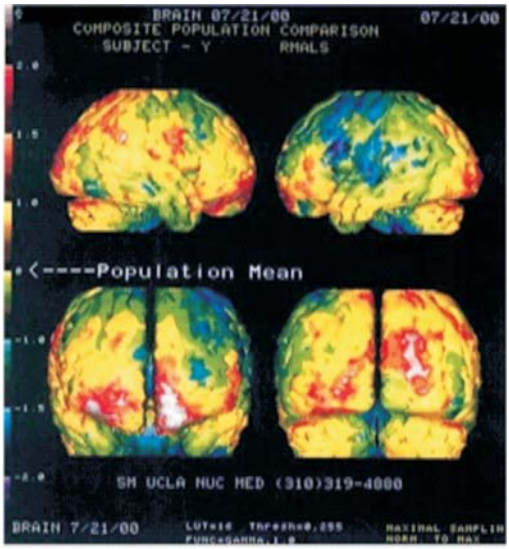
The amount of cocaine absorbed by the digestive route varies between 20% and 30% (Verebey, Gold 1988)

Holmstedt B, Lindgren J, Rivier L, Plowman T (1979) Cocaine in blood of coca chewers, J. Ethnopharm. 1: 69-78
Wilkinson P, Van Dyke C, Jatlow P, Barash P, Byck R (1980) Intranasal and oral cocaine kinetics, Clin. Pharmacol. Ther., 27: 386-394
Cone EJ (1995) Pharmacokinetics and pharmacodynamics of cocaine, J. Anal. Toxicology 19: 459-478
Jenkins A, Llosa T, Montoya ID, Cone EJ (1996) Identification and quatitation of alkaloids in coca tea, Forensic Science International, 77:
179-189
Llosa T, Chang-Fung E (2007) Efficient Absorption of oral cocaine contained in coca poder: a new form of use oral cocaine in Andean regions, NIDA/CPDD 69th meeting, Quebec City, Canada, June 16-21

TOXICOLOGY

The intestinal absorption of cocaine alkaloid can be detected in urine after 15 minutes and up to 72 hours.
Because cocaine is detected in the urine in very small amounts usually analyzes its metabolite benzoylecgonine (BE).
1 gram of crushed coca leaves containing a mean of 5 mg of cocaine alkaloid (Siegel et al 1986; Jenkins et a al 1996), and immerse in hot water (as coca tea) can release up 4 mg of cocaine alkaloid (Jenkins et al 1996).
After 10 hours of consumption of 1 cup of coca tea containing a mean of 4 mg of cocaine, urine of subjects showed levels between 3940 ng/mL of BE, and 4979 ng/mL of BE (Jenkins et al 1996).
Patients treated with agonist therapy with oral cocaine usually show BE urine levels above 50,000 ng/mL (range 30,000 to 100,000 ng/mL). When relapse during treatment BE urine levels usually exceed 100,000 ng/mL and could reach a million ng/mL of BE.

The detection of BE in urine is evidence of cocaine use and/or relapse in patients. BE negative urine results is evidence of abstinence in patients under treatment. However in patients treated with oral cocaine BE presence in urine is a sign of compliance the treatment, because under agonist oral cocaine schedule always the urine appear positive to BE. While under treatment schedule, dosing negative BE indicate that the patient is not complying with the treatment. The control of BE in urine can not be taken as an indicator of relapse or withdrawal in patients receiving oral cocaine agonist treatment.
Patients under oral cocaine agonist treatment should be follow up mainly with clinical, behavior and social controls.



Siegel RK, ElSoholy MA, Plowman T, Rury PM (1986) Cocaine in herbal tea, Letter to Editor, JAMA, January 3, Vol 255, N° 1
Verebey K, Gold MS (1988) From Coca Leaves to Crack: the effects of dose and routes of administration in abuse liability, Psych Ann 18: 513-520
Jenkins A, Llosa T, Montoya ID, Cone EJ (1996) Identification and quantitation of alkaloids in coca tea, Forensic Science International, 77: 179-189

EFFICIENT METHODS TO EXTRACT COCAINE FROM COCA LEAVES AND COCA POWDER

The amount of cocaine extracted from the leaves as coca tea vary when prepared with hot and cold water as well as the cocaine extracted from coca flour varies whether or not mixed with an alkaline substance (sodium bicarbonate, lime), which is evidenced the levels of BE in the urine of volunteers, as shown in Table below (Llosa, Chang-Fung 2007).

Dose CCP(2)	Dose CAlk (3)	Substance and Supplement	pH	BE level (1) At 10 hours	t-Student
5 g	25 mg	CCP mixed in cool w ater (200 mL) during 5 minutes	6.0	6003 ng/mL	
5 g	25 mg	CCP mixed in hot water (200 mL) during 5 minutes at 100° C	5.5	31142 ng/mL	p< 0.05
5 g	25 mg	CCP contained in gelatin capsules drink with a cool water (200 mL)	5.5	7769 ng/mL	
5 g	25 mg	CCP mixed with cool water (200 mL) plus 1 g sodium bicarbonate (4)	7.5	27100 ng/mL	p< 0.05

C(1) Quantitative Urine Benzoylecgonine level (Axsym/Abbott) (2) Coca Powder (3) Cocaine Alkaloid (4) NaHCO3 (pH 8.6) CCP plus NaHCO3 (5/1) (pH 7.5-8.0)

Llosa T, Chang-Fung E (2007) Efficient Absorption of oral cocaine contained in coca powder: a new form of use oral cocaine in Andean regions, NIDA/CPDD 69th meeting, Quebec City, Canada, June 16-21

Coca powder plus sodium bicarbonate

TOXICITY AND LIABILITY

References of oral cocaine use (as alkaloid) have shown that traditional doses do not produce intoxication, behavioral disorders or lead to addiction (Kantak 1975: Carroll 1977; Weil 1978; Siegel et al 1986).

An anecdotal reference by Siegel et al. in 1986 reported intoxication in a subject who ingested 80 coca tea bags (400 mg of cocaine) mixed with alcohol. He presented with elevated blood pressure and tachycardia for two hours. Laboratory studies showed no physiological, behavioral disturbances nor toxicity effects in volunteers that ingested 400 mg of cocaine hydrochloride in gelatin capsules by oral route (Walsh et al 2000).

There are no reported cases of abnormal or addictive behavior nor reports of deaths in sporadic or chronic users of oral cocaine by chewing, drink as infusions or eat as coca powder.

There are many references of acute intoxication and death when the plastic little bags contained hydrochloride coccaine are ingested by mouth for narcotic traffic purposes (body packers), and broken into the intestine (Wetli 1981).

Kantak KM (1975) Nutrition, nutrients and cocaine. In: Biochemistry and physiology of substance abuse. Botanical Museum Leaflets, Washington

Weil AT (1978) Coca leaf as therapeutic agent. Am Journal Drug Alcohol Abuse, 5 (1) 75-86

Wetli CV, Mittleman RE (1981) The body packer syndrome, Toxicity following ingestion and illicit drug packaged for transportation. J. Forensic Sci. 26: 492-500

Siegel RK, ElSoholy MA, Plowman T, Rury PM (1986) Cocaine in herbal tea, Letter to Editor, JAMA, January 3, Vol 255, N° 1

EFFICIENT WAYS TO OBTAIN THE ORAL COCAINE FOR AGONIST THERAPY

Llosa T, Chang-Fung E (2007) Efficient Absorption of oral cocaine contained in coca powder: a new form of use oral cocaine in Andean regions, NIDA/CPDD 69th meeting, Quebec City, Canada, June 16-21

For obtain 50 mg of cocaine alkaloid should be boiled 12 bags of 1 gram of crushed coca leaves (**coca tea bags**) in 500 ml of water for 5 minutes (for obtain 100 mg must boil 25 tea bags in 750 ml of water). To get the nutrients from the crushed leaves should be squeezed the bags before disposing. You can add sugar to the tea before drinking it or drink it raw. It is advisable not add any acid substance in order not to lower the pH and reduce absorption.

Coca powder can be eaten alone or mixed with food or liquids such as juice. For obtain 50 mg of cocaine alkaloid mix 12 grams of coca flour (a tablespoon full) with 5 gram of sodium bicarbonate (or equivalent alkaline substance) to obtain the alkaline pH of the mixture. If coca flour diluted in milk should be added sodium bicarbonate too. To obtain 100 mg of cocaine alkaloid must mix 2 tablespoons /25 gram) of coca powder wit 10 cc of sodium bicarbonate.

TREATMENT OF COCAINE DEPENDENCE

After 100 years of experimenting with several biological treatments the FDA nor other international health organizations worldwide has approved any drugs to control addiction to cocaine (Vocci, Elkashef 2005). The results have mainly served to reveal the substances that are not effective compared with placebo or control group. Only a few have shown some positive effects (Llosa 2007).

Vocci F, Elkashef A (2005). Pharmacotherapy and other treatment for cocaine abuse and dependence. Curr Opin Psychiatry 18: 265-270
Llosa T (2007) Handbook of Oral Cocaine in Addictions, T.llosa (ed), Coca Medica, Lima

NIDA TESTED MEDICATIONS FOR COCAINE DEPENDENCE TREATMENT

Amantadine, Baclofen, Bupropion, Naltrexone, Propranolol, Tiagabine, Yohimbine, Dextrometorphan, Dronabinol, GBR12909 (Vanoxerine), LAAM, LY544344, Methamphetamine, Modafinil, Aripripazole, Buprenorphine, Clonidine, Naltrexone Depot, Selegiline, Topiramate, Desipramine,Disulfiram, Fluoxetine, GCP44352, L-DOPA/Carbi, Mecamylamine,Methylphenidate
N-Acetyl-aspartate, Atomoxetine, Bup/naloxone, Cocaine Vaccine, Progesterone, Sertraline, Venlafaxine, d-Amphetamine, Divalproex, Gabapentin, Hydromorphone, Lofexidine, Memantine, Methadone **(Ivan Montoya-NIDA/CPDD Meeting 2006).**

Other substances under investigation in the last years are N-acetylcysteine, Cabergolide, Ondansetron, Diltiazen, Reserpine, Selegiline, Vigabatrin, Oral Cocaine (Llosa 2007; Gorelick 2009)

Gorelick DA (2009) Pharmacologic interventions for cocaine, methamphetamine, and other stimulant addiction. In Ries RK, Fiellin DA, Miller SC, & Saitz R (Eds) Principles of Addiction Medicine, 4th edition, (Philadelphia, PA: Lippincott Williams & Wilkins), 2009, chapter 51, pp. 707-721.
Edens E, Massa A, Petrakis I (2009) Novel Pharmacological Approaches to Drug Abuse Treatment, in: Behavioral Neuroscience of Drug Addiction, DW Self & JK Staley (eds), Current Topics in Behavioral Neurosciences, 29:343-386.

ORAL COCAINE

Is the ingestion of cocaine through the oral route in the form of cocaine alkaloid as infusions, capsules, tablets, flour or cocaine hydrochloride in capsules. In the Andean regions the oldest form of oral cocaine use is by chewing (chacchado, accullico, picchado), and coca leaves infusions.

SUBSTITUTION THERAPY: definition

Substitution therapy («agonist pharmacotherapy», «agonist replacement therapy», «agonist-assisted therapy») is defined as the administration under medical supervision of a prescribed psychoactive substance, pharmacologically related to the one producing dependence, to people with substance dependence, for achieving defined treatment aims. Substitution therapy is widely used in the management of nicotine (nicotine replacement therapy) and opioid dependence (methadone, buprenorphine and LAAM) (**World Health Organization 2004**)

SUBSTITUTION THERAPY: criteria

The following criteria should be considered essential for a drug to be appropriate for substitution therapy **(WHO, Drug Substitution Project, Geneva, May 1995):**

1. It shows cross-tolerance and cross dependence with the psychoactive substance causing dependence.
2. It reduces craving and suppresses withdrawal symptoms.
3. It facilitates psychosocial functioning and improved health.
4. It has no short or long term toxic effects.
5. Affordable and available.
6. Does not grossly impair psychomotor functioning.
7. Less attractive for diversion than the psychoactive substance for dependence.

SUBSTITUTION THERAPIES: Types

(classification proposed by Llosa T, Llosa LM, 2005)

Substitution Type I- uses the same addictive substance (original) or combination in which the same substance is present but through another modality or route of administration, in order to change, reduce or control the addictive behavior or its damages. At this time, transdermal nicotine and oral cocaine are the unique substitute type I for agonist treatment.
Substitution Type II- uses a different substance (mainly synthetic) than the addictive substance but it is similar in its chemistry to the original substance, its equivalent but with less pharmacological, psychological and behavioral negative effects (methadone, buprenorphine, methylphenidate, amphetamine).
Substitution Type III- uses different substances to the above to control or attenuate the physiological and behavioral effects of the original addictive substance. This may includes a variety of agonist and antagonist substances, antipsychotics, anticonvulsants, lithium, disulfiram, antidepressants, antiparkinsonians, prophylactic antibody or vaccines, tiagabine, ibogaine, vigabatrin, or naltrexone.
Note: *Substitute I and II must meet the criteria of an agonist substance in all cases.*

ORAL COCAINE USED AS SUBSTITUTE TREATMENT

Cocalization method: natural cocaine (alkaloid) which can be extracted by chewing coca leaves, drinking coca infusions (teas) or ingesting food products containing powder/flour that is used as agonist substance (Llosa, Llosa 2005). During the cocalization therapy patient receiving the nutritional supplement containing the infusion or powder of coca leaves, besides the cocaine alkaloid. Currently its use is limited to Andean regions where coca products for oral and dermal use are legal and sold over the counter.

Cocainization method: cocaine hydrochloride has been used inside gelatin capsules for research purposes (Walsh et al 1998; Rush et al 1999; Walsh et al 2000; Filmore et al 2002), and potentially could be used as an agonist therapy out of Andean regions (Llosa, Llosa 2005). During cocainization therapy patients receive only the pure cocaine alkaloid or cocaine hydrochloride, without the nutritional supplement containing in coca infusion or fluor, but in a higher concentration of cocaine in less volume.

Walsh SL, Jufer R, Cone E, Bigelow GE (1998) Repeated dosing with oral cocaine in humans: pharmacodynamic and pharmacokinetic effects. CPDD 59th meeting, NIDA Res Mong Series 178: 218
Rush CR, Baker R, Wright K (1999) Acute physiological and behavioral effects of oral cocaine in humans: a dose-response analysis. Drug and Alcohol Dependence, 55: 1-12
Walsh SL, Haberny KA, Bigelow GE (2000) Modulation of intravenous cocaine effects by chronic oral cocaine in humans, Psychopharmacology 150: 361-373
Filmore MT, Rush CR, Hays L (2002) Acute effects of oral cocaine on inhibitory control of behavior in humans, Drug and Alcohol Dependence, 67: 157-167
Llosa T, Llosa LM (2005) Oral Cocaine as Agonist Therapy in Cocaine Dependence, CPDD 67th meeting, June

Typical way to chew coca leaves by Andean people and tourists

REFERENCES TO ORAL COCAINE EFFECTIVENESS

For thousands of years the Andean people have used oral cocaine contained in coca leaves (by chewing) or coca infusions (coca tea) without showing signs of mental, organic, intellectual or behavioral disorders.
After visiting Bolivia in 1975, Kantak suggested the use of chewing coca leaves to control cocaine addiction.
In 1986, Siegel et al., mentioned the use of coca tea infusions as cocaine substitute treatment in a hospital in San Francisco, CA.
In 1994 Llosa, published the results of the first study performed with oral cocaine (as coca tea) to control cocaine addiction.
In 1994 Llosa presented the results of the first double-blind trial as agonist therapy performed with oral cocaine as coca tablets.
In 1999 Walsh et al., demonstrated that oral consumption of cocaine in doses similar to those of the Andean users (400 mg daily, divided in 3 or 4 doses), does not produce abnormal physiological nor behavioral side effects.
In 2000 Hurtado-Gumucio, in Bolivia, reported that 50 coca paste smokers that chewing 100 to 200 g of coca leaf per week for a mean of 2 years substantially improved the mental health of one-third of patients and socioeconomic functioning of almost half (clinical nor toxicological data on cocaine smoking was no reported).
In 2005 Llosa & Llosa presented in the CPDD 67th annual meeting the review of oral cocaine as agonist therapy in cocaine dependence.
In a last reviews Gorelick (2009), Edens et al (2009), and Herin et al (2010) have already mention studies on oral cocaine as an agonist treatment to control cocaine dependence.

Kantak KM (1975) Nutrition, nutrients and cocaine. In: Biochemistry and physiology of substance abuse. Botanical Museum Leaflets, Washington
Siegel RK, ElSoholy MA, Plowman T, Rury PM (1986) Cocaine in herbal tea, Letter to Editor, JAMA, January 3, Vol 255, N° 1
Llosa T (1994) The Standard Low Dose of Oral Cocaine Used for Treatment of Cocaine Dependence. Substance Abuse, Vol 15 N° 4, December
Hurtado-Gumucio J (2000) Coca leaf chewing as therapy for cocaine maintenance. Am. Med. Interne, 151, B:44-48, Masson, Paris
Llosa T, Llosa LM (2005) Oral Cocaine as Agonist Therapy in Cocaine Dependence, CPDD 67th Annual meeting, June
Gorelick DA (2009) Pharmacologic interventions for cocaine, methamphetamine, and other stimulant addiction. In Ries RK, Fiellin DA, Miller SC, & Saitz R (Eds) Principles of Addiction Medicine, 4th edition, (Philadelphia, PA: Lippincott Williams & Wilkins), 2009, chapter 51, pp. 707-721.
Edens E, Massa A, Petrakis I (2009) Novel Pharmacological Approaches to Drug Abuse Treatment, in: Behavioral Neuroscience of Drug Addiction, DW Self & JK Staley (eds), Current Topics in Behavioral Neurosciences, 29:343-386.
Herin DV, Rush CR, Grabowski J (2010) Agonist-like pharmacotherapy for stimulant dependence: preclinical, human laboratory, and clinical studies. Ann N.Y. Acad Sci xxxx 1-25.

TREATMENT SCHEDULES
(Llosa & Llosa 2005)

Substance: cocaine alkaloid or cocaine hydrochoride
Route: oral exclusively
Vehicle: - coca tea, coca powder in meals or containing in gelatin capsules
- cocaine alkaloid or cocaine hydrochloride containing in gelatin capsules (are used in cocaine studies out of Andean regions as USA).

Doses: according to the daily dose consumed by the patient in a binge, but usually starts with 50 mg three times a day and after three days can be increased to 50 mg daily. According to symptoms doses can be adjusted up to 300 mg or more (400-500 mg) per day divided in three doses.

Consider the possibility of comorbidity. In such cases you must attach the appropriate medication to the other diagnosis.
During the first days of abstinence is common to see many emotional reactions as anxiety, depression, irritability, sleep disorders or desires or attempts to stop treatment. In such cases the therapist can temporarily attach a medication to control the symptomatology.
Having achieved the control of craving, withdrawal and relapses (usually accomplished during the first month) is recommended to continue treatment at least 6 to 12 months, according to the background.

Llosa T, Llosa LM (2005) Oral Cocaine as Agonist Therapy in Cocaine Dependence, CPDD 67th meeting, June 18-23

RESULTS OF 127 PATIENTS UNDER SUBSTITUTION THERAPY (COCALIZATION)
(Llosa T & Llosa LM 2006)

No.	Sub sex	drug	trial	oral coc dose	vehicle	time	r-avg(E)	r-avg(e)	year	Status
20	m	CCP	Open	20 mg	CCT	3 mo	12 .8 mo	4.8 mo	(1989)	Report
23	m	CCP	Open	17.7 mg	CCT	12 mo	4.35 mo	1.22 mo	(1994)	Published
8	m	CCP	Blind	60 mg	CCT-CT	5 wks	4.3 wk	0.7 wk	(1996)	Published
20	m	CCP	Open	60 mg	CT	3 mo	4.3 wk	0.3 wk	(1996)	Not published
20	m	CCP	Blind	20 mg	CT	4 wk	4.7 wk	1.18 wk	(2002)	Published
18	m	HCC	Open	100-300 mg	CCT	6 to 12 mo	3.0 wk	0.4 wk	(2003-05)	Not published
10	m	HCC	Open	100-500 mg	CCT	6 to 12 mo	2.7 wk	0.6 wk	(2004-05)	In review
8	m/f	HCC	Open	50-200 mg	CP	3 to 6 mo	3.3 wk	0.8 wk	(2006)	Published

CCP: coca paste HCC: hydrochloride cocaine CCT: coca tea CP: coca powder CT: coca tablets r-avg (E): relapse at entry (per week/ month) r-avg (e): relapse at end (per week/month) mo: month wk: week m: men f: female

Llosa T, Llosa LM (2006) Guía de la Terapia de Cocalización, T.Llosa & LM Llosa (eds), Coca Médica, Mayo, Lima

CONCLUSIONS

1. Orally cocaine contained in coca leaves has been consumed by Andean people for thousand years for work, social and spiritual purposes without users show signs of diseases and behavioral disorders.
2. The use of oral cocaine as agonist therapy meets the criteria for substitution (replacement) therapies.
3. The review of the use of cocaine by oral route as agonist therapy has demonstrated efficiency
   to control cocaine dependence.
4. As there is no treatment approved by the FDA or any health international institution to control cocaine dependence, agonist therapy with oral cocaine may be a good option in the Andean countries where oral cocaine-based products can be buy over the counter without restriction.
5. Outside the Andean region may be administered by mixing the cocaine with a substance that only release the cocaine in the intestine to be absorbed.
6. Whereas the coca tea and coca flour contain little cocaine per milliliter or per milligram requires large amounts of liquid or powder cocaine (cocalization therapy) which in some cases may limit their use (edema, hypertension, gastritis; taste of flour, etc). It would be preferable to administer pure cocaine alkaloid (not as hydrochloride) in gelatin capsules or tablets (cocainization therapy) mixed with a substance that prevents its use in other ways and other purposes.
7. Because there is currently no approved treatment for cocaine dependence, agonist therapy with oral cocaine (cocalization and cocainization schedules) should be seen as a safe and effective alternative and must be further developed international studies out of Andean regions.

The *Kintu,* coca leaves ritual, Andean regions
(M.Molina, Artist, Perú)

Luis M. Llosa, MD, Teobaldo Llosa, MD

In recent years agonist therapy have aroused much interest among clinicians and researchers for treating cocaine dependence. The use of cocaine by oral route as agonist therapy has been investigated since the 1980s and has demonstrated effectiveness in reducing the number of relapses and prolong and maintain abstinence in patients addicted to various forms of cocaine (cocaine hydrochloride , crack, coca paste).

In Peru the sale of products made from coca leaves for oral and dermal use is legal and no age restrictions. Currently infusions of coca (coca tea) and coca powder are used for treatment of cocaine dependent patients. In the 1980s, the psychiatrist Teobaldo Llosa began the use of oral cocaine for agonist treatment called Cocalization (Cocalización) and Cocainization (Cocainización) according to the form of oral cocaine use.

In this brief review Luis M. Llosa, psychiatrist, lists the main characteristics of agonist therapy with oral cocaine and presents the appropriate criteria for use in the treatment of dependence to cocaine.

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