Pharmacological treatment of substance dependence from a neuroscientific perspective (I): opiates and cocaine

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Tratamiento farmacológico de la dependencia de sustancias desde una perspectiva neurocientífica (I): opiáceos y cocaína

Summary

In this review paper it is intended to analyze the most recent publications on pharmacological treatment of drug dependences from a neuroscientific perspective. It has been divided into two parts, the first one focuses on the treatment of illegal substance dependence, specifically opiates and cocaine; and the second part deals with the pharmacological treatments of three substances, two legal drugs such as alcohol and tobacco, and a group of medications with abuse potential, benzodiazepines. In this first part the neuroscientific aspects (genetic, neurochemistry, circuits involved, neuroimaging and neuropsychological deficits) relevant to understanding the pharmacological treatment of the main drug addictions are summarized. The pharmacotherapies of opiate dependence, both for detoxification and for dehabituation, are then discussed. Finally, the main medications that have been proposed to treat cocaine dependence are also reviewed.

Key words: *Treatment. Psychopharmacology. Neuroscience. Substance-related disorders.*

Resumen

En este artículo de revisión se pretende analizar las publicaciones más recientes sobre el tratamiento farmacológico de las drogodependencias desde una perspectiva neurocientífica. Ésta consta de dos partes, una primera dedicada al tratamiento de la dependencia de sustancias ilegales, como es el caso de los opiáceos y de la cocaína, y una segunda parte en la que se aborda el tratamiento farmacológico de tres sustancias, dos drogas legales como el alcohol y el tabaco, y un grupo de fármacos, las benzodiacepinas, con potencial de abuso. En esta primera parte se realiza un resumen de aquellos aspectos neurocientíficos (genética, neuroquímica, circuitos implicados, déficit neuropsicológico y neuroimagen) determinantes para comprender el tratamiento farmacológico de las principales drogodependencias. Posteriormente se aborda el tratamiento farmacológico de la dependencia de opiáceos, tanto de la desintoxicación como de la deshabituación, terminando con una revisión de los principales fármacos que han sido o están siendo propuestos para el tratamiento de la dependencia de la cocaína.

Palabras clave: *Tratamiento. Psicofarmacología. Neurociencias. Trastornos por uso de sustancias.*

INTRODUCTION

Substance dependence is a problem which, as the main diagnosis or as dual diagnosis, occurs more and more in the psychiatric practice. The World Health Organization defined dependence as a syndrome manifested by a behavior pattern in which the use of a substance has more priority than other behaviors. This establishes this disorder as a repeated impulse to commit oneself to low productive behaviors, a growing tension until the behavior is performed, and rapid disappearance of the tension when it is carried out[1].

Until a relatively short time ago, substance abuse was considered a field reserved to psychological and social investigation, both in regards to etiopathogenic understanding as well as treatment. This viewpoint of drug dependences has radically changed in the last 20 years for several reasons:

1. Animal models having high validity have been created.
2. The circuits involved in the reinforcement-reward system and dependence have been defined.
3. Some of the genes that are related with the formation of such circuits have been defined.

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4. It has been possible to study the brain disorders presented by these patients both with neuropsychological tests as well as in studies with structural and functional neuroimaging tests.
5. Our knowledge on the action mechanism of the drugs that create dependence has improved, thus making it possible to design new drugs and improve the therapeutic protocols.

Without even trying to review the advances in each one of these fields, as this is not the aim of this article, we are going to briefly mention some of the findings in relationship with the therapeutic implications.

From a wide perspective of biology, the question to be answered in regards to drug dependences would be if there are biological factors that make us especially vulnerable to suffering this type of dependences. The reinforcement system, as the alarm systems, is philogenetically very old and the function of the genes, neurotransmitters and circuits involved in these reward mechanisms have remained almost invariable during evolution. The validity of the animal models of dependence is based exactly on this information: the tendency to redundancy in the evolution of the nervous system. This does not mean that they are not also fundamental cultural and learning aspects. What it points out is that prior to entering into the importance of these factors, we should know the general mechanisms of biological vulnerability to drug dependences.

Genetics

Although it has been known since old times that alcoholism has a high familial aggregation, only recently has it been confirmed that this is not due, at least exclusively, to learning factors but rather that there is a clear genetic component. More recently, molecular studies have focused on the role of the genes coding for dopaminergic receptors, especially D_2, that would be involved, above all, in the reward mechanisms. This has even led to a proposal of classifying alcoholism according to clinical severity and to the importance of this genetic component[2]. In recent years, there have been many studies that have found a relationship between certain allelic variants of the D_2 gene and substance abuse, not exclusively with alcoholism but also with cocaine, nicotine and heroin[3]. Although the genetic factors do not explain, for sure, all the variance of the phenotype, it is presently accepted that the presence of the allelic variant A_1 increases the probability of substance abuse. Thus, in a statistical analysis of these data, the conclusion is reached that the importance of the presence of this allele can account for 27% of the variance, 33% can be attributed to other genes and 40% to environmental factors[4].

Neurochemistry

Substance dependence has some circuits (extended amygdala) and some neurotransmission systems (fundamentally dopaminergic) that are keys to understanding these disorders. Independently of the effect of the substances on one neurotransmission system or another, the final effect of those that are capable of producing dependence is always, in the last place, on them.

The dopaminergic system has great importance in substance related disorders (SRD), since it influences several of the basic conditions of these disorders. Although it is presently questioned if this system is the only one that explains the addictive power of the drugs, since there are signs that both alcohol as well as cocaine and opiates act on other areas (prefrontal cortex above all) independently from the dopaminergic system, this continues to be basic in the rewarding properties of these substances due to their affect in the mesoaccumbens[5,6]. This neurotransmission system is also primary in the maintenance of consumption, in this case due to neuroadaptation mechanisms[7]. In the chronic administration of drugs, after their interruption, there is a decrease in the dopaminergic function, which seems to be related with the dysphoric symptoms and compulsive craving behavior of the substance(s) to which the subject is addicted[8].

Within the specific neuroscientific foundations associated to SRD, it must be emphasized that a second mechanism of neuroadaptation is also produced, which is that of sensitization, that is, a dopaminergic hyperfunction that is crossed between different substances[9]; furthermore, situations such as stress facilitate it. To finish adding complexity, it is suggested that the sensitization may also be based on associative learning between the drug and the specific context in which the consumption is produced. All this explains situations that were previously supposed to be related with psychosocial aspects, such as relapse in addiction through other substance(s) other than that or those that the subject is dependent on; with stressing situations; as well as after returning to the same setting in which the subject was an addict (sensitization of environmental context).

Besides craving, there is evidence on difference conditioning processes (stimulus-response and stimulus-reward learning) relevant in addiction, that are, to a certain degree, influenced by dopaminergic neurotransmission in mesostriatal areas.

In regards to the action mechanisms, in the first part of this article, we will focus on opiates and cocaine. In regards to the opiates, the principal effects occur through a family of specific receptors. Among them, the mu receptor involved in dependence as well as regulating analgesia, respiratory depression and constipation stands out. The first endogenous opioid, encephalin, was discovered in 1974 and made it possible to open the neurobiological pathway to understand addiction to opiates. At present, it is known that opiates also have a significant effect on the dopaminergic and noradrenergic neurotransmission systems, granting the addictive properties, as has already be pointed out, through the action of the dopaminergic ventral tegmental area neurons, that are projected to the cerebral cortex and limbic system.

The results of at least one study with positron emission tomography (PET) suggest that one of the effects of all the opiates is a decrease in blood flow in certain brain regions in dependent subjects[1]. Furthermore, they produce changes in the number and sensitivity of the opiate receptors, together with an increase in sensitivity of the dopaminergic, cholinergic and serotoninergic neurons. Finally, the effects on the noradrenergic neurons are probably principally responsible for the opiate abstinence symptoms and they explain the treatments with alpha-adrenergic agonist drugs.

In relationship to cocaine, its effect is related with the competitive blockage of the dopaminergic reuptake by the dopamine transporter, which leads to its increase in the space and produces greater activation of both the D_1 as well as D_2 receptors, but there are also proofs of certain action on the D_3[1]. Although it is believed that the behavioral effects are basically influenced by the dopaminergic reuptake blockage, cocaine also blocks the reuptake of noradrenaline and serotonine. These latter action mechanisms as well as the effect of cocaine on the blood flow and cerebral glucose consumption are receiving great attention in the specialized literature. PET studies on cocaine addicts show high dopaminergic activity of the mesolimbic system when the patients have craving. In patients in recovery, a lower capacity for the receptor to receive dopamine is observed in the PET, which is maintained for approximately one and a half years. The activity is at its lowest level and the risk of relapse is high between the third and fourth week.

Circuits involved

In this sense, abuse drugs are self-administered by the mammals due to their actions on the limbic system, which corresponds more to a functional than an anatomical concept. It is related with the control of emotional behaviors and participates in the maintenance of the inner environment through the autonomous and endocrine nervous system. Furthermore, certain limbic structures are keys in the cognitive processing and integration, especially in some learning and memory processes, as well as in the affective attribution of the stimuli. The mesolimbocortical reward brain circuit is established from the synaptic interaction of inter-associated neurons, and most of them are included in the regions of the limbic systems, with preference in the forebrain medial bundles, its origin and projection being in a retrocaudal direction of the nucleus accumbens, lateral hypothalamus and ventral tegmental area[5]. The nucleus accumbens is, without doubt, the best known of the parts of this system; it is made up of two well defined zones, the central or core and the cortex or shell. The differentiation is more functional than real, since both portions respond to appetitive or aversive stimuli, but in a different way. If the stimuli are unusual or unforeseen, there is an important response of the shell, but if the stimuli are common or foreseen, it is poor; however, the core responds to aversive or generic motivational stimuli. This different response suggests that the core participates more in the response and the shell in the learning.

It seems that there are other circuits besides the mesolimbocortical one related with reward that are managed by other neurotransmitters. Thus, there may be participation of a circuit that includes the nucleus accumbens and basal structures of the forebrain as well as the ventral pallidum, in which opioid peptides and the GABA system participate. A group of interconnected neuronal structures is also included. They are known as extended amygdala, that includes the central nucleus of the amygdala, the cortex of the nucleus accumbens, the bed nucleus of the stria terminalis and the unnamed sublenticular substance. All these structures participate partially or totally in the involvement of the signal caused by emotional effect of the acute administration of designer drugs. Passing from occasional consumption to dependence is accompanied by a progressively aversive sensation, that becomes more important as the tolerance decreases the acute effects of the drug and the neuroadaptation induces dependence[5,6,10].

Neuropsychologic deficit

The first neuropsychologic studies related with substance abuse were performed in alcoholic patients. In the 1960's and 1970's, the cognitive deficit of these patients became manifest after a series of studies, above all in frontal functioning tasks. This is what became known as «alcoholic dementia»[11], which we will briefly review in the following part of this article. Neuropsychologic investigations with other substances have verified the presence of a cognitive deficit also in the use of opiates (heroin) and stimulants (amphetamines, cocaine, crack). Thus, the present data clearly speak of a neuropsychological deficit in subjects with stimulant[12,13] and opiate abuse. The importance of these deficits does not have a mere theoretical interest but rather is involved in the ability of these patients to carry out rehabilitation programs[14].

Neuroimaging

The first structural neuroimaging studies have made it possible to verify the changes that are produced in the long term with substance consumption. The most consistent data appear in alcoholic patients who show signs of cortico-subcortical atrophy from maintained alcohol abuse for a period of 10 years[15].

Recent advances in functional neuroimaging have made it possible for psychiatrists to study directly the internal repercussion of the mental processes in live human subjects. As a result, the upper mental functions no longer must be deduced from behavioral observations and the cognition study can be carried out in human subjects[5]. On the other hand, a recent review on neuroimaging and drug dependence concludes that neuroimaging can contribute new knowledge on the neurobiological

disorder of drug dependences and contribute to the development of its pharmacotherapy[16]. Along this line, it is necessary to stress the importance of studies that use substance discrimination, that have so greatly facilitated the analysis of the actions of the ligands, thanks to their marked neurobiological specificity. These studies have made it possible to advance in the knowledge of the bases of transmission and transduction, transcendental in the mechanisms of appearance of tolerance and sensitization, and thus, of dependence[17], and have discriminated that the cerebral activation patterns associated to the craving responses that have been provoked by exposure to conditioned stimuli are not exactly the same as those that have been induced by the administration of the psychotropic substance itself. Thus, this deals with two states of differentiable activation that perhaps should be identified with a different name[16].

In summary, at present we already have solid knowledge on the psychobiolgical effects of the substances, both in their acute intoxication aspect as well as abstinence, that allows us to improve and understand the effect of the drug treatments that are basic nowadays in the approach to these disorders[18].

TREATMENT OF OPIATE DEPENDENCE

As in the other dependences, drug treatment of opiate dependence is only one part of the overall treatment, in which other important measures are necessary, such as individual psychotherapy, group therapy or social intervention[19]. However, on the contrary to the other substance that will be described in this article (cocaine), drug treatment of opiate dependence is agreed on and clearly established[19], as the recommendation of the National Plan on Drugs (1996) in Spain[20].

These patients should be approached from an integrating perspective that is generally divided into two phases. The first is detoxification, with a clear biological component and the second, dehabituation which was previously more psychosocial, but which has made important pharmacological advances in recent years.

The description of the principle articles that mention treatment of this dependence is given in table 1.

Detoxification

In spite of the unpleasantness for the patient, opiate abstinence is not a medical emergency[19]. Treatment of the abstinence syndrome can be considered from four approaches: symptomatic treatment (benzodiazepines, neuroleptics and others), treatment with presynaptic alpha$_2$-adrenergic agonists, administration of opiate agonist drugs (principally methadone) and ultrashort detoxifications with mixtures of different drugs, but which have the basis of precipitating an opiate abstinence syndrome with antagonists (naloxone and/or naltrexone) that is, in turn, approached with a combination of drugs.

Symptomatic treatment of the abstinence syndrome

The aim of this treatment is to decrease the intensity of the syndrome, relieving its symptoms and signs. To do so, treatment should be personalized, according to its presentation, the most frequent being the use of:

Benzodiazepines

Preference is given to those having a long half life as they present less risk of addiction, as is diazepam (40-80 mg/day) and clorazepate dipotassium (50-150 mg/day), in 3-4 oral doses, tapering the dose 10% every day, to discontinue the regime in 10-12 days.

Neuroleptics

Traditionally, the use of neuroleptic drugs such as clotiapine (20-40 mg/day) or levomepromazine (50-75 mg/day) orally and decreasing the dose with the same regime as with the benzodizepines has been proposed. However, scientific data that support the use of this group of drugs with this objective do not exist. In addition, it must be mentioned that this group of patients is especially sensitive to the adverse effects of neuroleptics. However, certain authors propose that atypical neuroleptics may be useful because of the possibility that part of the reinforcing effects of opiates may be mediated by both a dopamine dependent mechanism as well as by another mechanism that is independent of this neurotransmitter[21].

Others

Clormethiazole has also been used due to its sedative and hypnotic effects, however the side effects and risk of dependence make its use as a baseline drug unadvisable. There are some recent studies that are investigating other possible drugs based on the action of the CBI cannabinoid system receptor antagonists[22], the selective guanylyl cyclase inhibition of the locus coeruleus[23] or its inhibition by prostandoid EP(3) receptor selective agonists[24].

Treatment with presynaptic alpha$_2$-adrenergic agonists

The objective of these agonists is to stop the noradrenergic release of the locus coeruleus that characterizes the opiate abstinence syndrome[25]. The most important ones are clonidine[25], guanfacine and lofexidine[26], clonidine being the most used in our setting, while lofexidine is used most in anglo-saxon countries. There are different treatment regimes with clonidine, however two tendencies should be stressed, the oral route and transdermal patches[25,27-29]. In regards to the initial dose, this varies according to the studies[30-33], but 0.1 mg every 4-6 h is recommended. This can be increased according to the severity of the symptoms, but without exceeding 1.2 mg/day in out-patients and 2 mg in hospitalized ones[25].

TABLE 1. Treatment of opiate dependence

Detoxification process				
Treatment type	*Drug*	*Authors*	*Year*	*In favor (F) or against (A)*
Detoxification process				
Symptomatic	Neuroleptics	Callado LF, et al.	2001	F
	CBI receptor agonists	Rubino T, et al.	2000	F
	Selective inhibitir of guanylyl cyclase	Sullivan ME, et al.	2000	F
Alpha$_2$-adrenergic agonists	Clonidine	Spencer L, et al.	1989	F
		Burant D	1990	F
		Ling, et al.	1990	F
		Jaffe JH, et al.	1992	F
		Kleber HD	1994	F
		O'connor PG, et al.	1994	F
		Renner JA	1994	F
		Iszczor JA, et al.	1997	F
	Lofexidine	Callado LF, et al.	2001	F
Opiate agonists	Methadone	Lorenzo P, et al.	1999	F
Ultrashort detoxifications	Naltrexone	Chanmugam AS, et al.	2000	A
		Gerra G, et al.	2000	F
	Midazolame and propofol	Laheij RJ, et al.	2000	F
		Álvarez FJ, et al.	2001	F
Dehabituation process				
Opiate agonists	Methadone	Weddington W	1995	F
		Liu JG, et al.	1999	F
		Anderson IB, et al.	2000	F
		Hoffman RS	2000	A
		Eap CB	2000	F
		Eap CB	2000	F
		Kristensen O	2000	F
Opiate antagonists	Naltrexone	Wickler A	1976	F
		Wall ME, et al.	1981	F
		Kleber HD, et al.	1985	F
		APA	1995	F
		Iszczor JA, et al.	1997	F
		Santo-Domingo L	2000	F
Opiate partial agonists	Buprenorphine	Lewis JW, et al.	1983	A
		Fudala PJ, et al.	1990	F
		San L, et al.	1992	A
		Mello NK, et al.	1993	F
		Blennow G, et al.	2000	F
	Buprenorphine and naloxone	Newman RG	1994	F
		Jacobs EA, et al.	1999	F
		Rothman RB, et al.	2000	F

The transdermal pathway seems to be preferable to the oral one[25,27-29], as it maintains the most stable blood levels, however, since it requires 48 h to be effective, it should initially be complemented with oral clonidine. Treatment with alpha$_2$-adrenergics has a series of advantages and disadvantages[19]. As *advantages*: *a)* the dose required to inhibit the adrenergic release is independent of the seriousness of the addiction, and *b)* it has sedative and analgesic effects, that are not opiate type. *Disadvantages* would be: *a)* hypotension and bradycardia, so that blood pressure monitoring is recommended; *b)* contraindication in patients with renal failure, hypotension, arrhythmias, serious depressive background, pregnancy and serious organic disease; *c)* they are less effective in patients with recent treatment with tricyclic antidepressants[25], and *d)* and they do not control all the symptoms of the abstinence syndrome. Due to the latter disadvantage, it may be necessary to administer[25]: ibuprofen for muscular and joint pains, cyclopropamide for stomach cramps and benzodiazepines for anxiety and sleep disorders.

Replacement treatment

On the contrary to the treatment with the alpha2-adrenergic agonists, treatment of the abstinence syndrome with opiate agonists (methadone) varies according to dependence grade. Thus, 1 mg of methadone counteracts 4 mg of morphine, 2 mg of heroin or 20 mg of meperidine. Four grades of severity of the abstinence syndrome are established, administering 10-15 mg of methadone in grade 1, 15-20 in II, 20-25 in III and 24-45 in IV, according to the severity of the picture. At times, larger doses are necessary. Once the symptoms and signs stop, the dose should be progressively decreased by 10% every two days, discontinuing it in a maximum period of 20 days[19], although normally it is achieved in 7-10 days. Urine study is recommended during this period to detect the consumption of psychoactive substances.

Ultrashort detoxifications

This technique is defined by rapidly obtaining, in a maximum of 24 hours, the optimum clinical control of the abstinence signs and symptoms as well as its perception by the physician and patient[34]. At present, there are no reliable studies regarding this type of treatment in which the drugs used for detoxification (clonidine) and dehabituation (naltrexone) are used jointly[19]. Although the production of rhabdomyolisis has been described with the use of subcutaneous naltrexone[35], it has been demonstrated that the ultrashort detoxifications that include naltrexone[36] are more effective than those that only use clonidine. When it is aimed to use superficial sedation, they are combined with intermediate half life benzodiazepines, while if the objective is anesthesia, midazolame together with propofol are generally used[34,37].

The different types used are the following: «home» detoxifications, in which professional health care workers give the patient and his/her supervising person the instructions and medication to perform the treatment; outpatient detoxifications, when they are performed in an out-patient center with supervision by health care professionals; detoxifications in day hospital, where the sedation is not very intense and intensive care or anesthesia service is not required; hospital detoxification under sedation, where monitoring and the collaboration of the service are required due to the intensity of the sedation and hospital detoxifications under anesthesia, as the previous, but also requiring intubation due to more important sedation[34]. In relationship to home and out-patient subtypes, the existence of serious side effects as well as that unforeseen in the evolution, and the presence of residual symptoms, make it necessary to perform more rigorous studies that make it possible to make these subtypes a safer practice. Thus, most of the authors propose using the hospital modalities with sedation or anesthesia[38,39].

Regarding the inclusion criteria, it should be considered that this technique is shown to be more effective in patients who suffer severer abstinence syndromes and who have suffered multiple failures with the conventional detoxification protocols, while it has been shown to be less effective in patients who come from methadone maintenance programs (MMP)[40].

Dehabituation

The pharmacological treatment of opiate dependence may be posed from three different viewpoints: replacement treatment with opiate agonist (methadone), treatment with opiate antagonists (naltrexone) and treatment with opiate partial agonists (buprenorphine)[41]:

Replacement treatment with opiate agonists

Methadone is a synthetic opiate that aims to substitute some of the effects of heroin and can be taken orally[1]. Its use was begun in the treatment of opiate dependence in the year 1964, in the Rockefeller Institute of New York, since it was observed that, on the contrary to other opiate agonists, methadone did not require an indefinite increase of the dose and did not produce euphoria when administered orally. At present, it is the most widely studied[42-45] and used opiate for the drug treatment of opiate dependence[19]. The clinical use of methadone is regulated through MMPs. In the beginning, these programs were classified in those that used low doses (up to 40 mg) and those that used high doses (up to 75 mg), but they are not presently classified in this way, since there are patients who do not become stabilized and it is necessary to use higher doses (greater than 80 mg). Before a patient is admitted in a MMP, a «therapeutic contract» is signed between the health care center responsible persons and the patient, in which the patient accepts its rules. In the strictest MMP, if the patient does not comply with the rules, he/she is given a thirty day period to change his/her behavior and if this is not done, the patient is expelled. In these programs, only 10% of «dirty» urines (positive to psychoactive substances) are tolerated.

The best candidates for these programs are: *a)* heroin addicts having several years addiction, with repeated failure in other treatments; *b)* patients affected by serious organic diseases; *c)* pregnant heroin addicts, or *d)* heroin addicts with psychiatric disorders[19]. Individualization of the dose is very important since it has been demonstrated that if they are lower than necessary, the risk of consumption of other substances and even program dropout increases. These doses not only depend on the biological characteristics of each individual but it has also been demonstrated that they depend on environmental factors, which influence the plasma levels of methadone[46]. However, monitoring these levels is not recommended[47]. It is recommended to begin with 30 mg as initial dose and to increase it between 5-10 mg until obtaining stabilization, generally with 60-100 mg[25,48].

In relationship to treatment time, it varies according to the patients, it being more and more frequent to give

preference to quality of life. Thus there is no specific period, but rather it is adapted to the objective established by the therapists and patient. These objectives should also be individualized according to the seriousness of the addiction and destructuration of the surroundings, racial factors[49] as well as the existence of psychiatric or organic comorbidity. There are considered to be three basic objectives: *a)* damage reduction: it consists in trying, with the help of the MMP, to make the patient capable of minimizing risk behaviors such as those that lead to HIV infection; *b)* dehabituation, with which it is aimed to decrease the methadone dose until the patient is prepared to discontinue it and go on to a drug free program, and *c)* rehabilitation, that aims to have the patient adapt to the surroundings and acquire adequate permanent psychosocial stability, without an established time limit. When it is decided to suspend treatment, it is recommended to reduce 5 mg per week in order to end the program in three or six months. Finally, the advantages and disadvantages derived from the MMPs can be stressed[1,19]. As advantages, it stands out that: *a)* greater retention of patients is permitted in comparison with other programs; *b)* it favors the decrease of risk of HIV infection due to discontinuing the intravenous route and it prevents other organic diseases derived from heroin consumption, decrease the risk of death[50]; *c)* it does not cause euphoria or does so minimally, and does not produce drowsiness or depression in prolonged treatments; *d)* it permits the rehabilitation of the patient, social reintegration and abandoning of criminality, thus the quality of life is greater[50]; *e)* decrease in criminal acts[50], and *f)* it does not change cognitive motor functions, the differences observed with the controls being due principally to sociodemographic factors[51]. On the other hand, there are some disadvantages, such as: *a)* continuing with an addiction, speaking pharmacologically, to opiates, with its dependence and abstinence; *b)* some of these patients consume other drugs; *c)* the treatments may be lasting and relapses are very frequent; *d)* a black market of me-thadone may appear[50], and *e)* there are sometimes side effects such as excess of dysphoresis, constipation, decrease in libido, sleep disorders, etc.[50,52]. Thus, the MMPs should be considered as a possibility in the treatment of opiate dependence, and are very effective in certain patients.

Treatment with opiate antagonists

Opiate antagonists block their effect, without causing dependence as they have no narcotic effects and do not cause euphoria or tolerance[1,53]. There are two antagonists that should be differentiated, naloxone, used to revert overdosage by its shorter mean life (30 min-1 h) and to be used parenterally[19]; and naltrexone, used for the treatment of the dependence, objective of this article, due to its longer half life (72 h)[1] and to being used orally[19]. Nalorphine and cyclazocine were used previously, but presently they are discarded due to their debatable efficacy and side effects[19].

Naltrexone is a pure competitive opiate antagonist, principally of the mu opiate receptors, and to a lesser degree, of the kappa and delta receptors[54]. The objective is to achieve blockage of the effects of exogenous opiate consumed, which facilitates the extinction of the desire conditioned by the positive reinforcement provoke by the substance and thus there is a gradual extinction of the self-administration of the opiate behavior[55,56]. Naltrexone is effective orally, with rapid and almost complete absorption, close to 96%, although it experiences a first step metabolism on the hepatic level so that between 5 and 60 % reaches the systemic circulation without changes[53,57].

There are few side effects with the usual doses of naltrexone and, in general, they are mild, appearing the first days of treatment and serious adverse reactions are rare. The side effects observed with naltrexone seem to be similar both in alcoholics as well as opiate addicted subjects[58]. The adverse reactions recorded most frequently during treatment with naltrexone are the following[58-60]: gastrointestinal discomfort, as nausea, vomiting, abdominal pain, diarrhea or constipation; neuromuscular and neuropsychiatric problems, as headaches, vertigo, nervousness, restlessness and irritability, asthenia, fatigue and dejection, anxiety, drowsiness, difficulty in falling asleep, joint and muscle pain, thoracic pain; sensation of cold, nasal congestion, sweating and tearing. Some of these symptoms may be confused with the opiate abstinence syndrome. They generally disappear several weeks after treatment onset.

We should keep the interaction that it produces with other therapeutic opiates (analgesics, antitussigenic, antidiarrheic, etc.) in mind as they compete with them for the occupation of the receptors. Certain care should also be taken when using naltrexone with other drugs having potential hepatic toxicity, as is the case of paracetamol or disulfiram or with oral hypoglycemics. However, the concurrent use of naltrexone with antidepressants seems to be safe.

Similarly to the MMPs, the results of treatment with naltrexone greatly depend on the correct indication. It has been observed that the patients who have some of the characteristics listed in the following are the ones who will benefit most from treatment with naltrexone.

Admission criteria: a) patients with a short evolution of opiate dependence; *b)* individuals with high level of motivation for abstinence; *c)* patients who are very aware that they want to interrupt treatment with methadone; *d)* patients with stable employment; *e)* patients who have left or who remain in protected therapeutic institutions (hospitals, jails, therapeutic communities, etc.), and *f)* addicts with recent relapses, after long abstinence periods, or who, for any reason, increase their risk[19,61,62].

Exclusion criteria: 1) pregnant patients or with risk of pregnancy due to its possible teratogen potential; 2) existence of renal failure, hepatic failure and/or acute hepatitis, because naltrexone is extensively metabolized in the liver and principally eliminated through the urine, recommending regular laboratory controls of hepatic

function during the treatment, and 3) hypersensitivity to naltrexone or any of its active ingredients.

There is a consensus[19,55,63] on the phases that the programs with naltrexone should follow, although there are different protocols. These programs should be made up of three phases:

1. *Induction*. This first phase may last from a few days up to approximately 2 weeks. The duration will be determined fundamentally by the present clinical characteristics of the patient, and specifically, of the patient's present consumption of opiates, since an opiate free period is necessary before initiating maintenance treatment with naltrexone in order to prevent the precipitation of an abstinence syndrome. Thus, among the various clinical conditions, we can find patients with present consumption of heroin, in MMP, with active abstinence syndrome, abstinent patients with relapse risk, etc.
   Usually, an alpha2-adrenergic agonist such as clonidine, that makes it possible to begin therapy with naltrexone as soon as the detoxification is complete, is generally used for the previous detoxification, reducing the opiate free period and thus the risk of illegal opiate consumption[64]. After the first days of waiting, an induction dose of 0.8 mg. of subcutaneous naloxone is begun with to see if there are positive symptoms of abstinence syndrome. If there are none in one hour, antagonization with naltrexone is begun, verifying that there are also no abstinence symptoms. The initial dose recommended is 12 mg (1/4 of the dose) of naltrexone, waiting one hour in case these symptoms appear. If they do not appear, another 25 mg. are administered. The initial standard dose that is generally given on the 2nd or 3rd day of induction is 50 mg/day orally, its increase being unnecessary[25].
2. *Maintenance*. The maintenance dose is 50 mg/day, however there are different treatment guidelines to reach the total recommended dose of 350 mg/week[55,63]: *a)* 50 mg/day orally, 7 days a week, recommended for the initial phases of the treatment, in cases when it is necessary to assure contact of the patient with health care personnel; *b)* 50 mg/day Monday to Friday 50 mg/day, and 100 mg on Saturday, or *c)* 100 mg Monday and Wednesday, 100 mg together with 150 mg on Fridays. If the patient tolerates it well and presents good motivation for the treatment, it is advisable to go on to administration of three times a week as soon as possible.
   A dose of 150 mg in a single day should not be exceeded since a superior incidence of side effects has been observed[65].
3. *Stabilization*. We should avoid failure, paying attention to its principal causes: *a)* symptoms of prolonged abstinence. These are more frequent in patients who come from MMP due to its greater half life, and these symptoms should be treated early with clonidine; *b)* craving, it being necessary to act with adequate use of free time, principally at night and week ends; *c)* degree of compliance, key factor in treatment success, that is obtained by taking the drug in front of the center's dispensing staff or by some family member taking responsibility, recurring in some cases to legal or work pressure, and *d)* the type of support therapy, in which the psychological and social techniques should achieve a change in the style of life and adequate structuring.

Finally, the principal advantages and disadvantages of the treatments with naltrexone as well as some of the possible solutions of the disadvantages are summarized. Within the advantages, the following stand out: *a)* that it does not produce dependence or abstinence syndrome; *b)* its half life is long, its administration is oral and it presents a wide safety margin; *c)* its side effects are few, and *d)* in theory, it reverts the endogenous opiate production deficit secondary to opiate dependence. Of the disadvantages, the following stand out: *a)* need to require a drug free period to prevent abstinence syndrome; *b)* it has a lower retention index than methadone, this being from 20-30 %; *c)* the increase of hepatic transaminases that it causes, and *d)* the relative elevated economic cost. To increase the retention index, correct selection of the patients included is recommended, since the subcutaneous implant of naltrexone implants did not show any advantages.

Treatment with opiate partial agonists

Buprenorphine hydrochloride is a semisynthetic opiate with partial agonist and antagonist properties that possess a potent analgesic action as other opiate agonists such as morphine. It was synthesized in 1968 and was proposed as a medication for the treatment of opiate dependence in 1978[66]. Together with its use for opiate dependence and neoplastic pain, its usefulness in cocaine dependence has been proposed[66,67]. Buprenophrine presents good absorption by the different administration pathways except orally. Its absorption is rapid after intramuscular injection, reaching maximum plasma concentration at 5-10 minutes of its administration[68]. Absorption by sublingual pathway is slower, achieving maximum plasma concentrations at 90-120 minutes after administration. The sublingual pathway presents a pure agonist effect at doses under 6 mg, while at doses above 8 mg, there can be antagonist effects, and it can precipitate into an abstinence syndrome, which would reduce the risk of overdose[69].

Buprenorphine presents high affinity both with opioid *mu* as well as kappa receptors and a lower affinity for the delta opioid receptors[70,71]. The high affinity of buprenorphine for the *mu* receptor seems to partially explain the long duration of the analgesic effects caused by this drug[72]. On its part, the opiate antagonist properties of buprenorphine are similar to those of naltrexone, and can be used in opiate dependence as well as detoxification and also in maintenance programs.

Although it has been proposed that only some mild abstinence symptoms appear on suddenly stopping buprenorphine administration after chronic consumption

in comparison with the marked abstinence symptoms observed with heroin, methadone or morphine[66], different studies have described an abstinence syndrome and an abuse potential similar to that of other opiate substances[73]. Abstinence symptoms associated with buprenorphine are maximum at 3-5 days after stopping its consumption and generally last 8-10 days[74].

The advantages that are derived from treatments with buprenorphine are: *a)* oral or sublingual administration pathway; *b)* limited psychtomimetic effects[75]; *c)* less abuse capacity than other agonists; *d)* wide safety margin[75], and *e)* mild and short abstinence syndrome[75]. However, it presents side effects such as sedation, nausea and vomiting. The doses used for treatment of the abstinence syndrome range from 2-8 mg/day. There are many studies[19] that compare efficacy of buprenorphine with that of methadone and naltrexone in the treatment of the dependence, showing initial retention rates superior to those of the programs with naltrexone and at least similar to those of MMPs, with doses of 8 mg/day. The most recent studies support the efficacy of the combination of buprenorphine and naloxone, in capsules that alternate the buprenorphine doses daily[76-78], although more studies that verify this regime are necessary[79].

Finally, it should be stressed that the advances in the knowledge of the production mechanism of opiate dependence are causing an important increase of studies on new substances that may be useful in this treatment[42,80].

TREATMENT OF COCAINE DEPENDENCE

At present, there is no agreement on the treatment of cocaine dependence[81], however there are recent advances in both the pharmacological as well as psychotherapeutic treatment that are useful in the management of these patients, the combination of both being recommended. The objectives of these therapeutic approaches aim to maintain the patient in treatment, achieving abstinence and preventing relapse.

The continuous advance in the knowledge of the action mechanisms of cocaine has meant a series of expectations and investigations aimed at improving the pharmacological approach to these patients[82-94]. The main function of the drugs used is found in the maintenance of abstinence, applied in combination with psychosocial approaches.

There are many drugs that have been used in the treatment of cocaine dependence (antidepressants, dopaminergic agonists, etc.) and they have different action mechanisms. Those described in the following are the ones that have demonstrated their efficacy most widely. The description of the principal articles that make reference to the treatment of this dependence are specified in table 2.

Antidepressants

The action mechanism that justifies the use of antidepressants is that long term cocaine consumption causes a dopamine, noradrenaline and serotonin deficit as well as hypersensitivity of the post-synaptic receptors. Thus, antidepressants would block the re-uptake of these neurotransmitters together with hyposensitization of the receptors[82-86,88,89]. Within the antidepressants, the tricyclics, above all desipramine, stand out for being the first to be used[81]. This drug has been effective in patients with specific disorders of depression and cocaine consumption, but also in those who do not suffer depression, and also reduces cocaine craving, and thus facilitates abstinence in dependent subjects. Decrease of craving has been demonstrated in open studies when it was used along with psychotherapy; its efficacy in the decrease of depressive symptoms and signs was also de-

TABLE 2. Treatment of cocaine dependence

Type of treatment	*Drug*	*Authors*	*Year*	*In favor (F) or against (A)*
Antidepressants	Tricyclics	Levin FR, et al.	1991	A
		San L et al.	1999	F
	SSRI	Bano MD, et al.	1999	F
		McDowell DM	2000	F
Dopaminergic agonists	Bromocriptine	Caine SB, et al.	2000	F
	Ecopipam	Romach MK, et al.	1999	F
	Pergolide	San L, et al.	1999	F
Opiate agonists/antagonists	Methadone	San L, et al.	1999	F
Mood estabilizing agents	Carbamacepine	San L, et al.	1999	F
CNS stimulats	Methylphenidate	Castañeda R, et al.	1999	F
	Baclofen	Brebner K, et al.	2000	F
Others	L-tryptophan	San L, et al.	1999	A
	Anticocaine antibodies	Fox BS	1997	F
		Mets B, et al.	1998	F
		Kantak KM, et al.	2000	F
	Labetalol	Soufuoglu M, et al.	2000	F
	Piperazines	Lewis DB, et al.	1999	F

monstrated when it was used without associated psychotherapy, both in cocaine as well and phencyclidine dependence. Controlled studies have demonstrated that the use of desipramine and bromocriptine is also effective, facilitating abstinence on decreasing dysphoria. In this type of studies, it has been observed that desipramine is more effective than lithium and the placebo in treatment retention, decreasing craving and contributing a greater percentage of abstinence. In a study by Kosten, a 44% percentage of abstinents was obtained in the patients treated with desipramine compared to 27% in the patients treated with placebo. However, other studies[95] having greater rigor have questioned the efficacy of this tricyclic antidepressant as improvements are not found in either craving or psychiatric symptoms. In opiate dependent patients in maintenance with agonists (MMP), desipramine has been shown to be effective in decreasing craving and dysphoria as well as in the decrease of cocaine use. It has also been shown to be more effective than amantadine and fluoxetine in the retention rate and in urine controls for cocaine and opiates. However, monitoring the plasma concentrations of this antidepressant is recommended in these patients to achieve greater efficacy of it. The doses used vary from 150 to 200 mg. The main disadvantage of treatment with desipramine is the 2-3 week period necessary for the drug to be effective as well as the elevated drop-out rates (20-50%) during this initial period[81].

Within the selective serotonin reuptake inhibitors, fluoxetine has also been demonstrated effective in decreasing cocaine consumption and craving. These results were also obtained in opiate dependents in MMP without producing alterations in the methadone concentrations and the fluoxetine was well tolerated. Decrease in the use of cocaine and a change in its consumption route from injected to smoked was achieved in these patients[96]. The doses that have shown greater efficacy range from 20 to 40 mg during 12 week periods. The most recent study on treatment of cocaine dependence with antidepressants[97] has demonstrated that venlafaxine, a wide spectrum antidepressant, is effective in those patients diagnosed of depression who did not tolerate desipramine, or in those in which the latter was shown to be ineffective. Thus, its utility in the reduction of the symptoms of mood state, as well as reduction in cocaine consumption in a percentage over 75%, have been demonstrated. The dose used was 150 mg for 12 weeks.

However, the existence of other studies that have questioned the use of these antidepressants has stimulated multiple research studies to search for other more effective antidepressants. Some of these studies have failed, such as those that have aimed to use mazindole, which presents drug interaction with cocaine, as well as the risk of increasing craving. Although phenelzine has been shown effective in the correction of the biochemical defects caused by prolonged cocaine consumption (dopaminergic, noradrenergic and serotoninergic depletion), its use is not recommended due to the risks that the MAOIs present, since they can cause hypertensive crisis if they are used with cocaine. Due to this interaction, its use has been proposed as an aversive agent[81]. On the contrary, others, such as doxepin, maprotiline, bupropion,trazodone, ritanserin and sertraline, initially appear to be useful.

Dopaminergic agonists

Justification for the use of dopaminergic agonists is found in the depletion of dopamine in the CNS caused by the prolonged consumption of cocaine. It is this depletion that causes craving, and the need to consume cocaine again in an attempt to increase the synaptic dopamine. It has recently been demonstrated that both the D_1 as well as D_2 receptors participate in the cocaine action mechanism, although in a different way[98,99], and thus, the use of agonists in cocaine dependence treatment should take this difference into account. The first studies that included dopaminergic agonists for the treatment of cocaine dependence used bromocriptine. This is a postsynaptic D_2 agonist and weak D_1 antagonist, that does not share the noradrenergic or serotoninergic agonist effects of cocaine. These initial open studies demonstrated their efficacy against craving, anergy and depression observed during the cocaine abstinence syndrome. After, controlled studies verified that craving decreases, but the Brief Psychiatric Rating Scale also does so. It has also been demonstrated to be effective if used together with desipramine and in MMP patients. The doses used go from 1.25 mg twice a day to 2.5 mg three times a day.

Although some initial studies showed that amantadine, an indirect dopaminergic agonist that causes dopamine release, was more effective than bromocriptine, controlled studies have found that although it is initially effective, after the initial 15 days, it is no longer more effective than the placebo. Furthermore, it has been demonstrated that it can increase reactivity to consumption stimuli.

Another dopaminergic agonist studied is pergolide, whose efficacy has not been completely established, but it can be useful since it seems to be a safe drug[81]. Lisuride or the combination L-dopa/carbidopa have also been studied, but their effectiveness has not been demonstrated.

Opiate agonists/antagonists

In MMP patients, it has been demonstrated that the increase of the methadone dose (opioid agonist) favors cocaine abstinence in 80% of the cases compared to 33% of the cases if we decrease it[81]. Opioid antagonists such as naltrexone have also been studied. Although its use was initially proposed as a blocker of the euphoric effect of cocaine, it was later demonstrated that its greatest utility is its capacity to decrease cocaine consumption, obtaining lower positivity in the urine controls, as was mentioned recently by San[81]. Good results have been obtained with buprenorphine, achieving treatment retentions superior to 91% at 12 weeks, observing a decrease

in opiate dependents, both in the use of opiates as well as that of cocaine. While it seems that there are no differences in efficacy between these opioids, differences really exist in regards to their doses, the use of high doses (65 mg of methadone or 12 mg of buprenorphine) being preferred compared to the use of low doses.

Mood stabilizer agents

Although some authors consider that the administration of Lithium can be contraindicated in cocaine dependent patients, it has been demonstrated that it is a very effective drug in those patients with bipolar or comorbid dysthimic disorders, which means 20-30% of the cocaine dependents.

The use of carbamazepine is justified by the hypothesis that craving may be a neurophysiological manifestation of the *kindling* phenomenon, however the results obtained are not very conclusive. Thus, while some seem to demonstrate its efficacy in the decrease of the number of positive urine controls to cocaine, others show negative results. A recent study, referenced by San[81], has observed that a dose of 400 mg/day and plasma concentrations of this drug correlate with a reduction in the positive urinary measurements of cocaine, with a decrease in craving, the number of consumption days and greater treatment retention. It also seems that carbamazepine decreases cocaine use in patients included in MMP. Regarding these therapeutic functions of carbamazepine, the possibility of its abuse in some subgroups of alcoholic or toxicomanic patients, its possible hematological side effects, as well as an increase in the cardiovascular effects of the cocaine must be mentioned.

CNS stimulants

Methylphenidate or pemoline cannot be considered an effective treatment as they do not improve cocaine abstinence, worsen some of its manifestations, and in the case of pemoline cause hepatotoxicity. However, the efficacy of the long acting CNS stimulants in treatment of cocaine dependence in patients with attention deficit has been demonstrated[100], these patients accounting for 17-40 % of the dependents on this substance[101-104], since cocaine means large amounts of beneficial effects for their symptoms and signs[101-104]. It has also been demonstrated that treatment with these CNS stimulants is not necessarily contraindicated because of cardiovascular toxicity or due to the drug abuse potential[105]. However, it has also been observed that CNS depressants such as baclofen, a GABA-B agonist, lessens the reinforcement effects of cocaine, however, its effectivity has only been observed in consumption of low doses of cocaine in animal research[106].

Other substances being investigated

Some authors recommend the use of neurotransmitter precursors, alone or in combination with antidepressants, for the treatment of cocaine dependent patients, however their efficacy has not been demonstrated. Those studied most are L-tryptophan, serotonin precursor, and L-tyrosine, dopamine and noradrenaline precursor, with the hypothesis that they facilitate or induce synthesis and the restoration of the depleted deposits of the previously mentioned neurotransmitters. However the existence of the eosinophilia-myalgia syndrome caused by the use of tryptophan makes their use in cocaine dependents unadvisable[81]. Another one of the presently studied approaches consists in the use of anti-cocaine antibodies to give rise to immunity to its psychostimulant effects[107,108]. Studies with the MO240 antibody and the IPC-1010 vaccine only demonstrate their efficacy when the antibody levels are sufficient[109] and, thus, periodic and frequent vaccination will be necessary for protection against this type of substance as it is neither immunogenic nor antigenic alone. Symptomatic treatment of the physiological and subjective effects of smoked cocaine has also been investigated[110] by use of labetalol that lessens the increases of cardiac rhythm and blood pressure caused by cocaine consumption, although it does not act on the subjective effects. Other substances that are presently under investigation are oxygenated analogues of 1-(2-[diphenylmethoxy]ethyl) and 1-(2-[bis[4-fluorophenyl]methoxy]ethyl)-4-(3-pehenylpropil) piperazines (GBR 12935 and GBR 12909)[111]. The hypothesis on which their use is based is their capacity to bind to the dopamine transporter and inhibit reuptake of ([3]H)-labeled dopamine. Although these studies have been performed in monkeys, they mean important advances for esterification and formulation of new substances in the treatment of cocaine dependence. There are many more substances that are under investigation[81,112,113] (flupenthixol, buspirone, gepirone, ondansetron, nifedipine, amperocide, hydrochloride of m-chlorophenylpiperazine, phenfluramine, disulfiram, alpha-methyl-paratyrosine, baclofen, etc.), however no conclusive results are available as of yet.

In any event, it should be stressed that the combination of psychotherapeutic treatments together with the previously described psychopharmacological ones has relevant importance in the approach to this condition, it being necessary to development specialized treatments for the different subtypes of cocaine dependent patients[81,114,115]. However, more controlled and randomized studies are still needed to evaluate the efficacy of these treatments[81]. In this sense, studies that analyze the influence of some of the psychosocial factors that participate in the evolution of the treatment of these patients are necessary: as the poor prognosis of the youngest, as well as those who do not complete secondary studies, the importance of the absence of axis I disorders, of initiating psychosocial treatments[116] and of race, studied by the racial identity attitude scale[117]. The most recent studies have attempted to compare the efficacy of different psychotherapies[118,119], although there is no consensus on which technique is most adequate since the results are dissimilar. The technique that has obtained the best re-

sults is that based on advise on drugs, both in their use on an individual level[120], as well as in groups[121], and both combined[122]. Although it has been shown to be more effective than individualized prevention of relapses in those patients who have not obtained complete abstinence, its efficacy is less in those in whom it has been achieved[121]. The best results have been obtained with the combination of the individualized form and in groups, surpassing cognitive and supportive-expressive psychotherapy, in the improvement of the addiction severity index-drug use composite score and in the number of days of cocaine consumption. Cognitive behavioral psychotherapy has also been demonstrated to be effective in the therapeutic approach to cocaine dependence, however while some studies considered it to be superior to 12 step facilitation therapy[123], others have demonstrated a similar effect[114]. Other psychosocial techniques with initially satisfactory results are those based on economic reinforcement[124], on social skills training and acquisition[125] and on therapeutic communities[126]. Finally, it is necessary to stress the importance of the new assessment techniques of the psychotherapists, such as the yale adherence and competence scale[127], and how beneficial their continuing training is considered to be[128].

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