Pharmacological treatment of substance dependence from a neuroscientific perspective (II): alcohol, benzodiazepines and nicotine

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Tratamiento farmacológico de la dependencia de sustancias desde una perspectiva neurocientífica (II): alcohol, benzodiacepinas y nicotina

Summary

The second part of this review deals with those neuroscientific aspects specific to the development and maintenance of dependence of three substances, two legal drugs (alcohol and tobacco) and a group of medications with abuse potential, benzodiazepines. Based on this context, the different pharmacological treatments of alcohol dependence, both related to detoxification and dehabituation, are discussed first. Treatment of the benzodiazepine withdrawal syndrome, together with the most outstanding aspects in the recent literature on relapse prevention, are reviewed. The publications on the treatment of nicotine dependence, both on replacement therapies and on bupropion, are analyzed. Finally, a critical reflection of the sources used to conduct this two-part review is done.

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

Resumen

En la segunda parte de esta revisión se abordan aquellos aspectos neurocientíficos específicos del desarrollo y mantenimiento de la dependencia de tres sustancias, dos drogas legales (alcohol y tabaco) y un grupo de fármacos, las benzodiacepinas, con potencial de abuso. A partir de esta contextualización se aborda el tratamiento farmacológico de la dependencia del alcohol, tanto de los aspectos determinantes en la desintoxicación como en la deshabituación. Luego se revisa el tratamiento del síndrome de abstinencia de benzodiacepinas, así como aquellos aspectos más destacados en la bibliografía reciente para la prevención de recaídas y se analizan las publicaciones referentes al tratamiento de la dependencia de nicotina, tanto de los tratamientos sustitutivos como de las aportaciones del bupropión. Por último, se realiza una reflexión crítica sobre las fuentes utilizadas para la realización de las dos partes de esta revisión.

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

INTRODUCTION

After the approach to opiates and cocaine dependence, two of the drugs that present the most clinical problems, we will study three substances, two legal drugs (alcohol and tobacco) and a group of drugs (benzodiazepines) with abuse potential, which have marked importance in the clinical practice.

As we saw in the first part of the review, our knowledge on the neurobiological bases of dependency has increased spectacularly in recent years. We have already mentioned the genetic, neurochemical foundations, the circuits involved, the neuropsychological deficits and the findings of neuroimagng in the first part. However, some brief specific clarifications should be made on the substances that we are going to refer to in this second part.

Of all the substances that affect the nervous system, alcohol is probable one of those for which we have the most extensive and detailed data, given its old and extended consumption. In acute intake, alcohol affects the nervous system as a depressor and can cause multiple behavior changes that go from mild disinhibition to coma. In chronic intoxication, there are numerous injuries to the nervous system and the behavioral and psychiatric changes that can occur are also very varied, going from delirium due to abstinence to global cognitive deterioration, that has been called alcoholic dementia[1].

Alcohol affects different neurotransmitters and brain receptors, among them dopamine, gamma-aminobuty-

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ric acid (GABA), glutamate, serotonin, adenosine, noradrenaline, and opioid peptides[2,3]. Furthermore, different neuroconductual effects of alcohol have been related with the development of dependence, among which stimulation, sedation, and the possibility of producing tolerance and abstinence stand out, without forgetting the relevance that the craving phenomenon, already described in the previous article, presents in the development of this disease[4]. In general terms, the pharmacological treatments of alcohol dependence will be divided into two large groups. The first is based on our knowledge of the pleasant and stimulating effects of alcohol that are mediated by a dopaminergic pathway and that is projected from the ventral tegmental area to the nucleus accumbens[5,6]. Excessive and repeated consumption of alcohol sensitizes this pathway and produces the development of dependence[7,8]. Drugs whose action mechanism acts on this system can reduce the alcohol reinforcing effects and thus reduce its consumption. The second group of drugs tries to counteract the reinforcing effect with an aversive effect to reduce consumption[9].

In relationship to benzodiazepines (BZD), these basically act on the receptor complex of the GABA that contains a chloride ion channel, a binding site for the GABA and a well-defined site for the BZD. When one of them is bond to the complex, the effect is an increase of the affinity of the receptor for the endogenous neurotransmitter GABA, and an increase of the chloride ion flow through the channel to the inside of the neuron, which is translated into an inhibitory effect. After prolonged consumption, the effects on the receptor are decreased, the key to this down-regulation not being a decrease in the number of receptors or of the affinity of the receptor for the GABA, but rather a deregulation between the GABA binding site and the chloride ion channel activation.

The addictive properties of nicotine reflect both its capacity to produce a positive reinforcement as well as to cause an abstinence syndrome when smoking is stopped after a chronic consumption period[10,11]. The capacity of nicotine to produce positive reinforcement seems to be caused, at least partially, by the stimulation and desensitization of a heterogeneous population of brain nicotinic receptors, especially in the mesolimbic dopaminergic system[12,13]. Thus, nicotine would share the capacity to stimulate the dopamine neurotransmission in the mesolimbic, and especially in the nucleus accumbens, with such diverse substances as alcohol, cocaine, amphetamine, cannabis, fentanyl, methadone, heroin, or phencyclidine[13-15]. On the other hand, the abstinence symptoms experienced by the smokers shortly after they have consumed the last cigarette seem to be mediated by hyperactivation in the locus ceruleus level of the noradrenergic neurons, and by the activity of the serotoninergic receptors (5-HT) in the dorsal raphe nucleus[16,17].

Alcohol shares the fact of being legal drugs in common with tobacco and with benzodiazepines and thus has a much more extensive consumption than the illegal drugs. This information partially explains the high comorbidity between the consumption of these substances and different psychiatric disorders. In recent years, neurobiological hypotheses that try to explain this high prevalence of dual diagnosis as a phenomenon that goes beyond the pure addictive effect of the drug and the high availability have been developed. These studies suggest that some individuals are dependent on these substances due to their use as self-medication of psychiatric disorders[18].

TREATMENT OF ALCOHOL DEPENDENCE

At present, it is considered that drug treatment, principally naltrexone and acamprosate, can improve treatment of alcohol dependence19, however this treatment must be combined with psychosocial therapy to promote emotional support, to approach psychological and social problems associated with alcohol dependence, and to increase drug treatment compliance. However, doubts still exist on the optimum dose of the drugs, treatment duration, the most adequate concomitant psychosocial therapy, cost-efficacy of the drug treatment, and the types of patients who would benefit from each specific drug[19].

There is presently a growing interest on the drug treatment for alcohol dependence[2,3,20]. This would consist of two clearly differentiated phases, as in the treatment of opiate dependence: detoxification and dehabituation. Detoxification improves the signs and symptoms of alcoholic abstinence; dehabituation helps the patient avoid future problems with alcohol.

The description of the principal studies used in this review for treatment of alcohol dependence is specified in table 1.

Detoxification treatment

Treatment of alcohol abstinence symptoms has two objectives. The first is to help the patient carry out detoxification as safely and comfortably as possible and the second is to promote motivation for the dehabituation treatment. Treatment may be as out-patients for those patients who have mild or moderate dependence and who do not suffer medical or psychiatric problems that advise hospital treatment. The regime can be performed with several drugs. Benzodiazepines[21] stand out in the first place, oral administration of chlordiazepoxide (50 mg/2-4 h) or diazepam (10 mg/2-4 h) being used until the symptoms are controlled. Clomethiazole, tetrabamate or tiapride can also be used, with clearly established regimes[22] of nine days for the first two and eight for tiapride. Serious abstinence of alcohol with delirium requires hospitalization in intensive care unit. In those cases in which serious alcoholic abstinence syndrome without delirium exist, the clomethiazole regime is twelve days, initiating with 16 capsules of 192 mg in four doses the first day. In these cases, treatment may be initiated intra-

TABLE 1. Treatment of alcohol dependence

Type of treatment	*Drug*	*Authors*	*Year*	*In favor (F) or against (A)*
Detoxification process				
Benzodiazepines	Chlordiazepoxide/diazepam	APA	2000	F
	Clometiazole	Sánchez-Turet M	1999	F
Dopaminergic antagonists	Tiapride	Peters DH, et al	1994	F
		Sánchez-Turet M	1999	F
Vitamins	Thiamine	Soler PA, et al	1999	F
Detoxification process				
Opiate antagonists	Naltrexone	Gessa GL, et al.	1985	F
		Hubber CL, et al.	1986	F
		Frochlich JC, et al.	1990	F
		Benjamin D, et al.	1993	F
		Chick J	1996	A
		Davidson D, et al.	1996	F
		Croop RS, et al.	1997	F
		Anonymous	1998	F
		Hersh D, et al.	1998	A
		Anonymous	1999	A
		Anton RF, et al.	1999	F
		Knox PC, et al.	1999	A
		Swift RM	1999	F
		Grinspoon L, et al.	2000	F
		O'Malley SS, et al.	2000	F
		Monti PM, et al.	2001	F
		McCaul M, et al.	In press	A
	Nalmefene	Mason BD, et al.	1994	F
		Anonymous	2000	F
Gamma aminobutyric acid agonist/N-methyl-D-aspartate antagonist	Acamprosate	Lhuintre JP, et al.	1990	F
		Samson HH, et al.	1992	F
		Ladwid D, et al.	1993	F
		Soyka M, et al.	1994	F
		Tsai G, et al.	1995	F
		Sass H, et al.	1996	F
		Whitworth AB, et al.	1996	F
		Geerings PJ, et al.	1997	F
		Poldrugo F	1997	F
		Foster RH, et al.	1999	F
		Dahchour A, et al.	2000	F
		Grinspoon L, et al.	2000	F
		Tempesta E, et al.	2000	F
Dopaminergic agonists/ antagonist	Tiapride	Peters DH, et al.	1994	F
		Shaw GK, et al.	1994	F
	Bromocriptine	Naranjo CA, et al.	1997	A
Aversive drugs	Disulfiram	Fuller M, et al.	1986	A
		Peachey JE, et al.	1989	A
		Hughes JC, et al.	1997	A
		Grinspoon L, et al.	2000	A
	Calcium cyanamide	Soler PA, et al.	1999	F
Others	Lithium	Dorus W, et al.	1989	A
		Lejeyeux M, et al.	1993	A
	Carbamazepine	Mueller TI, et al.	1997	F
	Benzodiazepines	Ciraulo DA, et al.	1998	A
		Addolorato G, et al.	2000	A
	SSRI	Naranjo CA, et al.	1986	F
		Gorelick DA	1993	A
		Naranjo CA, et al.	1994	F
		Naranjo CA, et al.	1994	F
		Kranzler HR, et al.	1995	A

venously and pass to orally at 24 hours[22]. In any case, and basically when faced with a picture of serious abstinence, attention must be given to hydroelectrolytic needs and 100 mg/day of thiamin should be administered intramuscularly to prevent neurological complications[23].

Dehabituation treatment

The drugs that have been shown to be most effective in the treatment of alcohol dependence are the following:

Opiate antagonists

The action mechanism that gave rise to clinical trials with opiate antagonists in patients with alcohol dependence was the observation that the mu agonists of the opiate increase alcohol consumption, and the antagonists reduce alcohol consumption in animals[24,25]. This has given rise to clinical trials on naltrexone, some of which are very recent[26], in patients with alcohol dependence. It has been proposed that naltrexone reduces alcohol consumption and increases abstinence by decrease of positive reinforcement, decreasing the intense desire to consume. The specific mechanism of this drug, as other antagonists of the mu-opiate, is to block alcohol induced dopamine release in the nucleus accumbens[27,28]. Furthermore, it reduces the desire to drink in both alcoholic patients[29] as well as social drinkers[30]. Several studies[24] have manifested that naltrexone is effective when psychosocial treatments are combined in alcohol dependence. However, other studies have not shown its efficacy[31-34], perhaps because they used very small groups or patients with multiple substance abuse[19]. It has also been observed that its effects stop shortly after finishing treatment and there are still no controlled studies that compare its efficacy with that of acamprosate[35]. An interaction between medication and psychotherapy has been shown[36]. In this sense, in the patients who do not consume alcohol, naltrexone increases abstinence in those allocated to receive supportive psychotherapy, but not among those assigned to psychotherapy designed to increase confrontation abilities. However, in the patients who consumed alcohol treated with naltrexone, confrontation psychotherapy was shown to be more effective than supportive psychotherapy to decrease the probabilities of experiencing a large consumption of alcohol[24].

The recommended dose for the first 90 days of abstinence is 50 mg per day, although from 25 up to 125 mg per day are used[19]. Adverse effects occur in 5-10% of the patients[37], the most frequent being nausea (10%), headaches (7%), anxiety (2%) and sedation (2%)[38]. Some of these adverse effects may be prevented and avoided, especially nausea[39]. It is necessary to consider the blockage of the opiate analgesic effect and the risks in hepatopathic patients, in whom periodic monitoring of the hepatic function during all the treatment is recommended[40].

Nalmefene, a mu and kappa-opiate antagonist, similar to naltrexone from the chemical point of view but less hepatotoxic[37,41], may also be effective since studies that have used it have shown greater abstinence in the patients treated than in those who were not treated[42,43].

Acamprosate

Acamprosate has an agonist activity of the gamma aminobutyric acid receptors[44] and an inhibitor activity of the N-methyl-D-aspartate (NMDA) receptors[45-46]. This drug normalizes the glutamatergic excitation that is produced in abstinence[47,48]. This effect could reduce the intense desire to drink and anxiety, and thus, it could decrease the need to consume[49]. The results of clinical trials have demonstrated that the efficacy of acamprosate doubles that of the placebo during a three month period[37,50-57], besides reducing hospitalization and rehabilitation costs[58]. The usual dose of acamprosate is 2-3 g per day in fractionated doses. This drug is not metabolized but rather is eliminated by the kidney, so that it should be cautious-ly administered to patients with renal function deterioration. Its principal side effects are headache (20%) and diarrhea (10%).

Dopaminergic agonists/antagonists

The action mechanisms that justify the use of these drugs are the blockage of the reinforcing effects of alcohol by dopaminergic antagonists[59] and relief of the deficiency state of the dopamine with the agonists[60]. Tiapride is a D_2 antagonist of dopamine that reduces alcohol abstinence symptoms, it being approved for the treatment of acute and chronic alcoholism[61]. Those patients who are being treated with tiapride have more probability of remaining abstinent and use the health care services less[62]. Bromocriptine was also studied, but did not demonstrate efficacy in the treatment of alcoholism dependence[63].

Aversive drugs

Alcohol is metabolized in two phases: ethanol is transformed by alcohol dehydrogenase in acetaldehyde and then the aldehyde dehydrogenase transforms the acetaldehyde in acetate. In most alcoholics, acetaldehyde is rapidly metabolized so that its accumulation does not cause symptoms such as tachycardia, rubefaction, diaphoresis, dyspnea, nausea and vomiting. Aversive drugs block this second phase, causing the accumulation of acetaldehyde that produces these aversive symptoms. The possibility of experiencing these unpleasant symptoms dissuades alcohol consumption. Disulfiram irreversibly inhibits aldehyde dehydrogenase. This was the first proposal of treatment[37], however controlled studies with this drug have not been sufficiently conclusive, it only being effective in men who consumed alcohol and then

felt bad, consumption only being reduced after the relapse[37,64-66]. The dose used is 250 mg per day, but the range varies between 125-1,000 mg, depending on the adverse effects and response. Disulfiram inhibits the metabolism of several drugs, especially anticoagulant drugs, phenytoin and isoniazid, exaggerating their effects, it being necessary to administer it with caution in patients with hepatopathies. It is contraindicated in pregnant women and patients with ischemic heart disease and it can also cause hepatitis. Hepatic controls must be performed with periodicity[19].

The other aversive drug is calcium cyanamide[67], which is, on the contrary, a reversible inhibitor whose effect appears at a few hours of its administration and disappears the following day. The dose used is 50 mg/12 h, in oral solution. As it does not produce inhibition of the dopamine-beta-hydroxylase enzyme, it does not interfere in dopamine metabolism and can be administered in active psychotic patients.

Other substances

Although there are many drugs that have demonstrated a reduction in alcohol consumption, the following have not been approved for the treatment of alcohol dependence. Within mood stabilizers, experiments have been done with Lithium, but it has not been demonstrated sufficiently effective[68,69]. However, carbamazepine[70] has been demonstrated effective, however the number of patients studied is insufficient.

Benzodiazepines, sedative drugs that are used for the treatment of the abstinence syndrome, have not been demonstrated effective to treat alcohol dependence, since there is a high risk that a dependence on them will be created[71]. However, it has recently been demonstrated that baclofen seems to be effective in the treatment of alcohol dependence[72].

Serotoninergic drugs have been tested under the hypothesis that serotonin could modulate the behavioral effects of alcohol, although their effects are complex due to the presence of multiple subtypes of serotonin receptors[73-75]. SSRIs, as fluoxetine, sertraline and citalopram, which increase serotoninergic function, decrease consumption[76,77], since they decrease liking and desire for alcohol[78] in heavy drinkers. However, conclusive results have not been obtained in the rest of alcohol dependent patients[79,80].

The most recent advances in the research on animals and patients promise a rapid advance and increase of the series of useful drugs in a near future to approach these patients. Buspirone, nefazodone, ondansetron and ritanserin seem to be effective in animals[81-83] but not in alcohol dependent patients[84-87]. Other substances under investigation are: acetyl-l-carnitine[88], dextromethorphan[89], MRZ 2/579 antagonist of the NMDA receptor[90] and hypericum extract[91].

If alcohol dependence occurs in a patient with some psychiatric disorder, reduction of the psychiatric disease symptoms can decrease the impulse of the patients to self-medicate with alcohol[32], it being recommended to include cognitive-behavioral therapies in the approach[92]. Under this hypothesis desipramine[93], imipramine[94] and fluoxetina[95] have been successfully tested in patients with depression; buspirone has been shown differently in the different studies on patients with anxiety[96,97]. Tests have also been done with gabapentin in patients with insomnia and alcohol dependence[98].

TREATMENT OF BENZODIAZEPINE DEPENDENCE

Several decades ago, the first benzodiazepine, chlordiazepoxide (librium 2960), was synthesized. Since then, more than 3,000 compounds have been created and more than one hundred have been marketed, the action mechanism being common for all of them[99]. The risk of abuse and dependence of benzodiazepines is real.[99] and should be identified by the clinician. An unsolved controversy is to assess this risk based on previous disorders of substance abuse and personality, as two factors which increase vulnerability individually or, frequently associated.

Regarding benzodiazepines, their clinical abuse is included in a section that includes disorders related with sedatives, hypnotics or anxiolytics. The benzodiazepines, object of this review, are the most used, but this section also includes barbiturics, which together with other substances having a similar action as metacualone, meprobamate and glutethimide, are in frank decline, both in their therapeutic use as well as abuse. That is why this review will focus exclusively on the benzodiazepines that are used therapeutically as anxiolytics, antiepileptics and anesthetics, as well as to treat alcohol abstinence.

Treatment of benzodiazepine dependence should be approached considering the following points: correct diagnosis of benzodiazepine dependence, treatment of the abstinence syndrome and prevention of relapses.

However, there is no generalized consensus on the most adequate therapy. Thus all the recommendations are based on clinical experiences, which, in turn, are based on the complicated mechanisms of development of benzodiazepine dependence[100-102].

The description of the main studies used in this review for the treatment of benzodiazepine dependence is specified in table 2.

Treatment of the abstinence syndrome

Once benzodiazepine dependence is diagnosed, abstinence is self-limited and evolves without complications in most of the cases[99]. From the pharmacological point of view, the guidelines that should be applied to treatment of benzodiazepine abstinence include: gradual decrease of dosage; substitution of benzodiazepines with other drugs having less addictive capacity; and simultaneously, introduction of non-pharmacological type treatment of anxiety.

TABLE 2. Treatment of benzodiazepine dependence

Type of treatment	*Drug*	*Authors*	*Year*	*In favor (F) or against (A)*
Gradual reduction	Long middle life benzodiazepines	Lader M	1989	F
		Lader M, et al.	1991	F
		Ashton H	1994	F
		Ashton H	1994b	F
		Lader M	1994	F
		Pertursson H	1994	F
		Ito T, et al.	1996	F
		Moro MA, et al.	1999	F
		Nelson J, et al.	1999	F
		Cervera G, et al.	2001	F
Partial agonist of benzodiazepinic receptor	Alpidem	Lader M, et al.	1993	F
Beta-blockers	Propranolol	Abernethy DR, et al.	1981	F
		Tyrer P, et al.	1981	F
		Cantopher T, et al.	1990	F
		Hallström C	1998	A
α_2-adrenergic agonist	Clonidine	Keshavan MS, et al.	1985	F
		Goodman WK, et al.	1986	A
		Rickels K, et al.	1999	F
Anti-convulsant	Carbamazepine	Klein E, et al.	1986	F
		Ries RK, et al.	1989	F
		García-Borreguero D, et al.	1991	F
		Schweizer E, et al.	1991	F
		Pages KP, et al.	1998	F
		Rickels K, et al.	1999	F
	Sodium valproate	Roy-Byrne PP, et al.	1989	F
		Apelt S, et al.	1990	F
		Rickels K, et al.	1999	F
Antidepressants	Trazodone	Ansseau M, et al.	1993	F
		Rickels K, et al.	1999	F
	Dothiepin	Tyrer P, et al.	1996	F
	Imipramine	Rickels K, et al.	1999	F
	Amitriptiline	Srisurapanont M, et al.	1998	F
Partial 5-HT_{1A} agonists	Buspirone	Schweizer E, et al.	1986	A
		Delle Chiaie R, et al.	1995	F
Barbituics	Several	Marks J	1988	F
		APA	1990	F
Hypnotics	Zolpidem/Zopiclone	Bottlender R, et al.	1997	A
Others	CCK-B antagonists	Chopin P, et al.	1993	F
	Abecarnil	Aufdenbrinke B	1998	F
	Neurosteroids	Olsen RW, et al.	1995	F
	Flumazenil	File SE, et al.	1987	F
		Savic I, et al.	1991	F
		Schweizer E, et al.	1998	F
		Gerak LR et al.	1999	F
	Pentadecapeptine	Jelovac N, et al.	1999	F
		Wala EP, et al.	1999	F
	Progesterone	Scheizer E, et al.	1995	A
	Diphenhydramine	Nath C, et al.	1997	F

The relationship of the principal drugs studied for the treatment of benzodiazepine abstinence syndrome are: antidepressants (tricyclics, atypical, SSRI and MAOIs), serotoninergic anxiolytics (5-HT_{1A} agonist and 5-$HT_{2/3}$ antagonists), anti-epileptics (carbazepine and valproic acid), CCK-B antagonists, steroid hormones with barbituric type metabolites, drugs active on benzodiazepinic receptor (partial agonists and antagonists) as well as other drugs.

Most of the authors[103-108] coincide in gradual reduction. They substitute the short or intermediate acting benzodiazepines, which are the ones that generate the most abuse and dependence problems, with one having a long half life in equivalent doses[99], as is represented in table 3, and then they make slow reductions.

During the treatment process, the use of evaluation scales on the intensity of the abstinence is recommen-

TABLE 3. Equivalent doses of the anxiolytic and hypnotic effects of the different benzodiazepines

Benzodiazepines	*Equivalent dose (mg)*	*Tablets/capsules (mg)*	*Oral solution (mg/ml)*
Chordiazepoxide	25	5, 10, 25	—
Diazepam	10	2, 5, 10, 25	2/5, 5/5
Lorazepam	1	1, 5	—
Lormetazepam	1	1, 2	—
Nitrazepam	10	5	2, 5/5
Oxazepam	20	10, 20	—
Temazepam	20	10, 20, 30	10/5

ded to assess the correct efficacy of the treatment[109]. Although there is no consensus on the existence of a first choice therapy for the treatment of the abstinence syndrome, it is considered that the long half life benzodiazepines are the drugs that have the greatest utility since they present crossed tolerance[110,111]. Since the frequency and seriousness of the abstinence symptoms are directly related with the rapidity of the decrease of the drug plasma concentrations, short half life benzodiazepines should be replaced by equivalent doses of other long-acting benzodiazepines[112] such as diazepam, which produces its effects quickly, it being effective both for its hypnotic as well as anxiolytic effect.

The partial agonists of the benzodiazepinic receptor should also produce improvement in the abstinence manifestations while the patient (and probably their receptors) adapts to the withdrawal of the benzodiazepines. However, the only pilot study published up to date in which the efficacy of alpidem is evaluated was negative[113]. Pharmacologically, the use of non-benzodiazepinic type drugs, such as propranolol, a beta blocker drug that has been tested to reduce intensity of abstinence symptoms related with hyperactivity of the vegetative nervous system, has also been proposed[114,115]. Although it has certain popularity in the clinical practice, this group of drugs does not seem to be very effective in the treatment of anxiety manifestations, above all if they are serious[116]. Propranolol has also been tested as a drug to maintain abstinence a decreasing doses[117].

Antipsychotics, also at low doses, can be effective to counteract abstinence manifestations, although, in practice, not all antipsychotics are useful. Although, in some cases, antipsychotics may be an alternative to treatment with benzodiazepines, the risk of side effects is excessive in relationship to the possible benefit that they can supply.

The use of clonidine in drug treatment of benzodiazepine abstinence[118,119] has also been studied, although with dissimilar results[120]. The base of its indication is the existence of noradrenergic hyperactivity similar to that produced in opiate abstinence in which clonidine has already demonstrated its efficacy, with the idea that reducing adrenergic activity would decrease the seriousness of the abstinence. The doses tested range from 0.4 to 0.6 mg/day and, in spite of prolonging the treatment for several weeks, its efficacy is practically null.

In addition, carbamazepine[119] has been tested as an anti-epileptic drug and to decrease CNS hyperactivity[121,122] in two open clinical trials[123,124] and in a placebo controlled double blind study in patients who took daily doses equal to or greater than 20 mg/day of diazepam[125]. In general, the beneficial effects may be considered as moderate in the control of the abstinence syndrome and somewhat better to avoid relapses. Sodium valproate also acts by increasing the gabaergic function and presents crossed tolerance with benzodiazepines, so that it seems to decrease the seriousness of abstinence[119,126,127].

Some antidepressant drugs such as trazodone[119,128], dothiepin[129], imipramine[119] or amitriptiline[130] have also been tested in the treatment of benzodiazepine dependence. An attempt has been made recently to develop new antidepressants that would present a better drug profile than the tricyclics, as is the case of the SSRIs and other third generation antidepressants such as venlafaxine, but their efficacy has not been sufficiently demonstrated.

Substitution of benzodiazepines with non-benzodiazepinic anxiolytic drugs such as buspirone does not eliminate or avoid the development of the abstinence syndrome[131]. Although this is a partial 5-HT_{1A} agonist anxiolytic, indicated in the treatment of generalized anxiety disorder, it has little prestige among the clinicians due to the delay in the onset of its action and because it does not present any of the qualities of the benzodiazepines, so that it is considered that this drug is not very effective in patients who have previously taken benzodiazepines. However, in a recent study, the patients previously treated with buspirone for several weeks before interrupting treatment with benzodiazepines showed a good response, although these users have a 5 month course of benzodiazepines[132].

The use of intermediate or long half life barbiturics may relieve the symptoms of abstinence, especially in patients with mixed benzodiazepines-alcohol dependence[133]. This type of treatments is performed better in the hospital setting, following the recommendations of the American Psychiatric Association[134].

Non-anxiolytic hypnotic drugs such as zolpidem or zopiclone also do not manage to revert the abstinence manifestations and cannot be considered as alternative drugs in the detoxification of the benzodiazepines, as cases of dependence have even been described[135].

Use of CCK-B antagonists has been proposed1 due to their possible modulating action on monoaminergic neurotransmission[36]. Another possible therapeutic strategy is the use of drugs that directly or indirectly increase gabaergic transmission, such as abecarnil type partial agonists[137] or neurosteroids with barbituric type activity[138]. In some case, it has been proposed to act directly on the benzodiazepinic receptor and some pilot studies on benzodiazepines tolerance or dependence have tested the treatment in epileptic episodes by the administration of the antagonist flumazemil[139-142], pentadecapeptine BPC 157[143] and PK 11195[144]. It is also believed that progesterone may be a promising drug since it presents metabolites that have a barbituric type modulating action in

gabaergic neurotransmission, however it was not shown to be effective in a controlled clinical trial[145]. Finally, another family of substances studied is that of sedative antihistaminics, with emphasis on diphenhydramine, which has been shown to be effective in the treatment of benzodiazepine dependence in rats[146] .

In patients with very high dose consumption, hospitalization is recommended to proceed to detoxification in case there are complications, for example, seizures, when the doses are decreased[99]. If these seizures occur and cannot be controlled, i.v. phenitoin can be used. Antipsychotics are contraindicated since they can worsen the symptoms. There is no consensus regarding the duration of the process, but decreasing the dose weekly in a period of approximately 6-8 weeks is generally recommended.

Prevention of relapses

It is difficult to evaluate the percentage of patients with benzodiazepine dependence who suffer relapses. This varies from one study to another, according to the selection criteria of the patients, but it is considered that there is a 20 % risk in the patients who begin treatment with benzodiazepines[147] and it is greater in those patients with frequent tendency to capsules consumption[148].

The best treatment, once again, is prevention, Moro et al.[99] recommend the following measures to avoid the relapses:

1. Individualize the dose for each patient, giving preference to the minimum doses[147], and carry out a strict control of the prescription to patients with indications, adopting a rational plan for the use of the drug, with short term objectives and periodic evaluation of the treatment efficacy.
2. Avoid consumption of other central nervous system depressants (alcohol, barbiturics, etc.) simultaneously.
3. Avoid sudden interruptions and recommend slow tapering of the drug, although it has been demonstrated that treatment duration has less importance in the abstinence pattern[106].
4. There is no clinical evidence that prolonged treatments (greater than four months) are more effective and there are even studies that indicate that prolonged use of benzodiazepines for years may worsen the anxiety state or insomnia. Use of long-acting half life benzodiazepines presents a superior margin of safety.
5. Do not prescribe benzodiazepines as antidepressants or analgesics, since they do not have these effects, and remember that drug therapeutics is only a part of the global strategy in the treatment of the anxious patient.

TREATMENT OF NICOTINE DEPENDENCE

Nicotine dependence makes up the most frequent psychiatric disorder and the principal avoidable cause of morbidity and mortality in Western countries[149,150]. It is estimated that 68.5 % of Spaniards between 15 to 65 years have tried a cigarette at some time and that 35-38 % smoke daily, 80 % of whom would be nicotine dependents[151]. There is a clear causal relationship between tobacco consumption and heart diseases, cerebrovascular accidents, other vascular diseases, different types of cancers, or chronic obstructive lung disease, and the harmful effects on pregnancy are also known[150,152]. Cigarettes contain more than 4,000 chemical elements, and at least 400 substances with clear carcinogenic effect. Among these, tar (associated to lung cancer), carbon monoxide and nicotine (cardiovascular diseases) as well as certain components and smoke particles that favor the appearance of respiratory diseases stand out[153].

Approximately 70% of smokers state that they want to stop and one third of adult smokers make a serious attempt to stop smoking per year; most try by their own means without formal treatment. A total of 75-80% of smokers have tried to stop at some time, 55% of them have never achieved it; only 5% of them who try it on their own account achieve maintained abstinence. Most of those who have stopped smoking need to try it several times until they achieve it[154].

Drug treatments for nicotine dependence can be divided based on the existing evidence on its efficacy into two large groups[154-155]:

1. First line treatments that would include nicotine replacement therapies (NRT) and bupropion.
2. Second line treatments, that include clonidine, nortriptyline or the combination of NRT. On the other hand, there are a series of drug agents that are presently under investigation and that may become useful in the treatment to stop smoking, as is the case of the anti-tobacco vaccine, methoxsalen, the nicotinic antagonist mecamylame and other metabolism inductors. The principle articles that have been used in this review to elaborate the treatment of nicotine dependence are specified in table 4.

Nicotine replacement treatment

Until very recently, drug treatment for tobacco dehabituation has been mainly focused on administration of nicotine by pathway differing from that of cigarettes consumption and with the use of a sufficient dose to decrease the abstinence syndrome. NRT may be used with all smokers who exceed 10 cigarettes per day, except in the presence of serious medical diseases that contraindicate it[154]. Replacement therapy has been developed by:

1. Nicotine patch. There are 16 and 24 hours presentations in 5-30 mg doses.
2. Nicotine gum. The usual dosage ranges from 2 to 4 mg.
3. Nasal spray. It produces very rapid blood levels and generates immediate relief of craving.
4. Oral inhaler.
5. Sublingual tablets.

TABLE 4. Treatment of nicotine dependence

Type of treatment	*Drug*	*Authors*	*Year*	*In favor (F) or against (A)*
Replacement treatment	Nicotine	Fiore MC, et al.	2000	F
		Silagy C, et al.	2000	F
		West R, et al.	2000	F
Atypical antidepressant/ controversial mechanism	Bupropion	Hurt RD, et al.	1997	F
		Hayford KE, et al.	1999	F
		Jorenby DE, et al.	1999	F
		Fiore MC, et al.	2000	F
		Shiffman S, et al.	2000	A
		Slemmer JE, et al.	2000	F
		West R, et al.	2000	F
		Dong J, et al.	2001	F
		Hays JT, et al.	2001	F
		McRobbie H, et al.	2001	F
		Tashkin DP, et al.	2001	F
		Tonstad S, et al.	2001	F
		Martínez-Raga J, et al.	In press	F
α_2-adrenergic agonist	Clonidine	Fiore MC, et al.	2000	F
		West R, et al.	2000	F
Typical antidepressant	Nortriptyline	Fiore MC, et al.	2000	F
		West R, et al.	2000	F

All the pharmaceutics formulations are equally effective and double the abstinence rate in comparison with the placebo. They decrease the nicotine abstinence symptoms and decrease craving for cigarrettes[154,156]. Global efficacy of NRT in controlled and randomized follow-up studies with at least 6 months of follow-up has been established in a recent meta-analysis in an abstinence rate of 13.9-23.8%, while the abstinence rates with the placebo after at least 6 months of follow-up in the studies included in the meta-analysis was 8.3-12.7%[156].

Adverse effects and contraindications

NRTs are generally well tolerated, their most frequent adverse effects being insomnia, irritation at the site of applications, headaches, nausea and rhinitis[154]. NRTs are contraindicated in patients allergic to the drugs and in individuals with a background of acute myocardial infarction, angina pectoris, serious cardiac arrhythmias or cardio- or cerebrovascular accidents. Furthermore, transdermal nicotine patches are contraindicated in patients with chronic dermatologic disease (psoriasis, urticaria or chronic dermatitis). NRTs are also contraindicated in individuals who are taking some α_2-adrenergic agonist (such as clonidine). It should also be avoided in pregnancy.

Bupropion

Bupropion is a new drug agent that has recently been approved for treatment of nicotine dependence in sustained release formulation[157], and whose efficacy and tolerance have been demonstrated in different double blind, randomized and placebo controlled clinical trials having more than six months of follow-up[158-163]. Bupropion is an atypical antidepressant that has been used for the treatment of depression in the United States of America since 1989, but not in Europe. The first suggestions of its possible use in the treatment of smoking arose from the anecdotal reports of smoking withdrawal in smokers who were taking the drug for depression. However, it has been described that it acts with equal efficacy in patients with and without a background of depression, which suggests that its action in the treatment of smoking is not due to its antidepressive properties[164].

Action mechanism

The exact action mechanism of bupropion in the treatment of nicotine dependence is unknown. Traditionally, this drug was listed as a weak inhibitor of noradrenaline and dopamine reuptake[165]. In this way, its effects on noradrenergic neurotransmission would be responsible for its effects on the nicotinic abstinence symptoms while its dopaminergic actions would affect the reinforcement capacity and the addictive properties of nicotine and would explain its apparent anti-craving effects. However, laboratory studies have not shown an effect of bupropion on nicotine craving[166] suggested by the clinical trials[159,163]. Based on these data and the neuropharmacological studies, an action mechanism of bupropion different from that originally proposed has been suggested[157]. On the one hand, a recent study has not been able to de-

monstrate any dopaminergic action of bupropion, while it suggested an effect on the release of noradrenaline and an activation of the serotoninergic system[167]. On the other hand, a non-competitive antagonist effect of bupropion in the nicotinic receptors has recently been described[168].

Pharmacokinetic characteristics

Orally, bupropion presents rapid and complete absorption, the maximum plasma concentration being observed at 3 hours of its administration[169]. Its metabolization is basically produced on the hepatic level, with the formation of three pharmacologically active metabolites. The mean half-life of elimination of bupropion is approximately 21 hours. Plasma concentration in stable state of bupropion and of its metabolites is reached after 5 and 8 days, respectively[169]. Thus, the patients should establish the date to stop smoking in the second week of treatment. The pharmacokinetics is similar in men and women, in elderly, as well as in smokers and non-smokers[169,170].

The initial dose of bupropion is one 150 mg tablet daily (administered in the morning) for the first 6 days, which should be increased, after the seventh day, to 150 mg twice a day, being administered with an interval of 8 hours. Doses greater than 300 mg daily should never be administered. Treatment with Bupropion should last between 7 to 12 weeks, although its duration will depend on the benefits reported and the risks it has for the patient[154,155].

Contraindications and adverse effects

Bupropion is contraindicated in patients with epileptic disease, as well as in other situations that may increase the risk of experiencing seizures, as is the case of present or past anorexia or bulimia nervosa, background of a tumor in the CNS, or in cases of sudden abstinence of alcohol or benzodiazepines. It is also contraindicated in cases of serious hepatic cirrhosis or in patients with bipolar disorder[171-173]. Furthermore, the simultaneous administration of bupropion and a monoamine oxidase inhibitor (MAOI) is contraindicated. On the other hand, the drug should be carefully administered in other situations that increase risk of seizures, such as in the case of other drugs that reduce seizure threshold, alcohol abuse, background of serious brain trauma or diabetes. It should also be avoided in general in pregnant or nursing smokers[174].

Bupropion is generally well tolerated, both in smokers of the general population[158-160] as well as in those with chronic respiratory disease[162] or with cardiovascular disease[161]. Its most frequent adverse effects are: insomnia, headaches, mouth dryness, nausea or constipation, although the only ones that are significantly more frequent at therapeutic doses (300 mg/day) than with placebo are insomnia and mouth dryness[159,160]. There is also a small risk of causing seizures, which is dose dependent, the risk at therapeutic doses of 0.1% being similar to that of other antidepressives[174].

CONCLUSIONS

As a final reflection, a last observation should be made, which can perfectly be extended to any psychodrug proposed for the treatment of any psychiatric disease. This observation refers to the quality of the clinical trials, recently reviewed by the American Society of Clinical Psychopharmacology Recommendations[175], and which discovers the lack of this type of studies. This review has used these recommendations for the reading and analysis of the articles, observing some of these deficiencies, which have made it necessary to complete the information with more sources other than the clinical trials as the previous reviews and expert's consensuses.

The relationship of the deficiencies described by this association[175] is diverse, but those that have been observed during the reading and analysis of the clinical trials used in this review can be emphasized. In the first place, it should be stated that some of the drugs proposed for the treatment of some specific dependence have been tested because they had previously demonstrated their efficacy in another dependence, which facilitates the trial and makes it safer, but does not offer real and significant therapeutic advances. In the second place, it should be stated that most of the articles published on some psychodrugs have given positive results, in some cases all, which not only may be due to its excellence but also because, on one hand, there is a tendency to accept the publications that go along this line and also because, as Kelin et al.[175] stress, the pressure of the competition in the pharmaceutical industry should be compensated with regulating efforts by the pertinent administrations. This last aspect refers to the fact that strategies such as shortening phase 2 of these studies, for example in which the therapeutic dose is decided, or the lack of information on results that are not so positive, do not help when determining the efficacy of a psychodrug.

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