Opioid Receptor Antagonists in the Treatment of Alcoholism

Los Antagonistas de los Receptores Opioides en el Tratamiento del Alcoholismo

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Abstract

Objectives: On the basis of the recent advances in drug therapy of alcoholism, we conducted a review on opioid receptor antagonist drugs with approved indication for the treatment of alcoholism, such as naltrexone and nalmefene. *Methods:* We reviewed over 100 publications on peptides and opioid receptors, as well as studies conducted in experimental animals and in humans on the effect of opioid receptor antagonists on alcohol consumption in the treatment of alcoholism. We also reviewed the pharmacological characteristics of naltrexone and nalmefene, and the usefulness of these drugs in clinical practice. *Results:* Much evidence has demonstrated the efficacy of naltrexone and nalmefene for the reduction of alcohol consumption, in experimental animals as well as in humans examined under experimental bar conditions; however, due to its different receptor profile, nalmefene has been associated with higher efficacy levels in reducing alcohol consumption in alcohol-dependent rats. In addition, a great number of controlled clinical trials have demonstrated the efficacy of naltrexone for relapse prevention in patients with an alcohol dependence disorder. Recent controlled clinical trials have demonstrated the efficacy of nalmefene "as-needed" in the reduction of alcohol consumption in subjects with mild alcohol dependence. *Conclusions:* Both naltrexone and nalmefene have proved to be safe, well tolerated, easy to manage, and efficient drugs for the treatment of alcohol dependence disorder (currently known as alcohol use disorder). On the basis of recent controlled clinical trials, nalmefene has been shown to result in a significant reduction of alcohol consumption, thereby representing a new objective that extends the therapeutic possibilities for those patients who do not wish for a continuous abstinence, but rather a reduction of alcohol consumption.

Key words: Nalmefene, naltrexone, opioid receptor antagonist drugs, alcoholism treatment, reduction of alcohol consumption.

Resumen

Objetivos: A partir de los recientes progresos en la farmacoterapia del alcoholismo, hemos efectuado una revisión sobre los fármacos antagonistas de los receptores opioides, que tienen aprobada la indicación para el tratamiento del alcoholismo, como son naltrexona y nalmefeno. *Metodología:* Hemos revisado más de 100 publicaciones sobre péptidos y receptores opioides, el efecto de los fármacos antagonistas de los receptores opioides sobre el consumo de alcohol, tanto en animales como en humanos, tanto en el laboratorio como para el tratamiento del alcoholismo. También se describen las características farmacológicas de naltrexona y de nalmefeno y su utilidad en la práctica clínica. *Resultados:* Múltiples evidencias han demostrado la eficacia de naltrexona y nalmefeno para reducir el consumo de alcohol, tanto en animales de laboratorio como también en personas estudiadas en situación de bar experimental, aunque debido al diferente perfil receptorial, nalmefeno ha sido relacionado con una mayor eficacia para la reducción del consumo de alcohol, en ratas que presentan dependencia del alcohol. Además, un gran número de ensayos clínicos controlados han demostrado la eficacia de naltrexona para la prevención de recaídas, en personas que presentan un trastorno por dependencia del alcohol. Ensayos clínicos controlados recientes han demostrado la eficacia de nalmefeno "a demanda" para reducir el consumo de alcohol, en personas que presentan un trastorno por dependencia del alcohol de baja gravedad. *Conclusiones:* Tanto naltrexona como nalmefeno han demostrado ser fármacos seguros, bien tolerados, de manejo sencillo, y eficaces para el tratamiento del trastorno por dependencia del alcohol, (actualmente llamado trastorno por consumo de alcohol). A partir de recientes ensayos clínicos controlados se ha comprobado que nalmefeno produce una reducción significativa del consumo de alcohol, lo cual supone un nuevo objetivo que amplía las posibilidades de tratamiento para los pacientes que no desean la abstención continuada, sino una reducción de su consumo de alcohol.

Palabras clave: Nalmefeno, naltrexona, antagonistas de los receptores opioides, tratamiento del alcoholismo, reducción del consumo de alcohol.

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Alcoholism. currently known as alcohol use disorder, is the most common mental disorder among men and one with more scientific research behind it than most, both in the laboratory with animals and, in terms of diagnosis and treatment, in clinical practice (Guardia Serecigni, Jiménez-Arriero, Pascual Pastor, Flórez Menéndez, & Contel Guillamón, 2008).

Alcoholism is an addictive illness, probably associated with a malfunctioning of certain brain circuits that play a role in behavioral self-control when consuming alcoholic drinks. It is characterized by incentive-motivational aspects of alcohol consumption and their conditioned stimuli, but also by a deterioration in the capacity to inhibit inappropriate responses in the search for and consumption of alcohol (Kalivas & Volkow, 2005). If the course of the illness is not stopped, its medical, psychiatric, addictive, work and social consequences may progressively worsen, contributing to increased risk of relapse and also to making the illness more chronic and perpetuating it (Guardia, Surkov, & Cardús, 2011).

The main symptom of alcoholism is the difficulty in controlling alcohol consumption. This is linked to the impaired functioning of various neurotransmitter systems, among which the glutamatergic, GABAergic, dopaminergic and opioid systems stand out. Preclinical research studies have provided a great deal of scientific evidence, which has later been confirmed in clinical practice and have been extremely useful in the development and pharmacological treatment of alcoholism (Guardia Serecigni, 2015).

The majority of pharmaceutical drugs which have been studied for the treatment of alcoholism did not reach clinical practice, given that the clinical tests carried out did not show them to be more efficacious than the placebo. Drugs which have not displayed clear efficacy against alcoholism include dopaminergic agonists and antagonists, glutamatergicc antagonists and $GABA_A$ agonists (Guardia Serecigni et al., 2008; Pascual, Guardia, Pereiro, & Bobes, 2013). The majority, though not all, of the clinical trials carried out in Europe of acamprosate demonstrated its efficacy against relapse, but the most recent tests in the USA were not able to confirm that this drug was better than the placebo (Anton, O'Malley, Ciraulo, Cisler, Couper et al., 2006). Furthermore, the daily dosage of 6 tablets makes compliance very difficult for alcoholic patients, and without good compliance a drug is unlikely to be efficacious. As regards topiramate, only two controlled clinical trials, directed by the same researcher, have provided results better than placebo (Johnson, Ait-Daoud, Bowden, Di Clemente, Roache et al., 2003; Johnson, Rosenthal, Capece, Wiegand, Mao et. al., 2007). What is more, no health authority has approved its use in the treatment of alcoholism.

Among the drugs whose efficacy has been demonstrated, and which have been approved for the treatment of alcohol abuse, the opioid receptor antagonist drugs naltrexone and nalmefene stand out. They have a complex scientific background, having been researched in heavy drinking animals (mice, rats, monkeys) as well as people in experimental bar type laboratory settings and through clinical trials on the treatment of alcoholism (Guardia Serecigni, 2015).

The action of opioid antagonists on alcohol consumption has played a decisive role in both the neurobiological understanding of alcohol addiction and in the pharmacological treatment of the disorder. Some laboratory studies, carried out in experimental bars, have helped us to understand how naltrexone and nalmefene work to reduce alcohol consumption in a drinking session. And many controlled clinical trials on alcohol abuse treatment have assessed its efficacy and tolerability. In the initial studies in the 1990s, the medication was administered daily with the aim of furthering continuous abstention, while in the most recent trials the focus has rather been on a reduction of alcohol consumption and the dosage regimen has changed to "as needed use", limited to the days or occasions in which the person decides to drink alcoholic beverages (Guardia Serecigni, 2015).

Many people who have had problems as a consequence of excessive alcohol consumption decide to stop drinking, even without the help of treatment, when these problems start to overwhelm them. Such people can go without a drink for several weeks and can remain in remission even for months or years if they take a specialized course of treatment. However, the day when they decide to have an alcoholic drink it is likely that they will have serious difficulties to control alcohol consumption and will again take to drinking excessively, and that this will be accompanied by a rapid reappearance of the negative consequences associated with this behavior. This typical relapse sequence usually happens one or more times during the recovery process of alcohol abuse patients. Nevertheless, it always comes as a surprise and a disappointment to close relatives, and can be devastating for the patient (Guardia Serecigni, 2011).

There are various treatments which help the patient to "stop drinking" and "stay dry" for a period, but it is likely that sooner or later the patient will try an alcoholic drink, and from this moment on their lack of control regarding alcoholic drinks will return. This is the so called deprivation effect, proven in both animals and alcohol dependent humans. This effect can be blocked by opioid receptor antagonist drugs (Sinclair, 1990; Sinclair, 2001).

Previously, the only accepted goal of treatment was complete and continued abstinence from alcoholic drinks. However, when the patient starts treatment, he/she generally does not have the clear intention to stop drinking entirely. Rather, it is common that patients try to stop drinking habitually but leave themselves the option of the odd

drink on a particular day or occasion that they clearly associate with alcohol. This is where a common misunderstanding between doctor and patient arises. The doctor believes that the patient is determined to stop drinking completely, because that is what he/she has said. But the patient, not knowing the real nature of the addictive illness he/she is dealing with, believes that a small amount of alcohol on a special day would not interfere with his/her recovery. The problem is that when the patient tries a small alcoholic drink, the loss of control returns and this can lead back to drinking excessively and the negative consequences associated with it (Guardia Serecigni, 2011).

In other words, the real treatment goal that alcoholic patients set themselves in the initial recovery phase does not coincide with the expectation of complete and continued abstinence held by their doctors, but rather with the new objective of a REDUCTION of alcohol consumption, which does allow for the occasional low-risk drink.

Neurobiology of alcoholism

Acute administration of alcohol facilitates the inhibitory activity of GABA, which together with a reduction in the excitatory activity of glutamate, calcium channels and noradrenaline, generate a slowing down of the central nervous system (CNS) which, in extreme cases of (alcoholic) intoxication can lead to coma and death from cardio-respiratory failure.

Meanwhile, chronic administration of alcohol results in compensatory neuroadaptive changes that generate a state of hyperexcitability in the CNS, which can manifest clinically in withdrawal symptoms and which is due to glutamatergic, noradrenergic and calcium channel hyperfunction as well as GABAergic hypofunction.

In the midbrain ventral tegmental area (VTA), the dopaminergic neurons are under tonic inhibitory control by GABA neurons, which in turn can be activated by the glutamatergic neurons or inhibited by opioidergic neurotransmission. The functioning of these neurotransmission systems, which come together at the VTA intersection, can play a fundamental role in relapse.

When alcoholic patients stop drinking, their dopaminergic neurotransmission is usually at low levels (a transitory state of hypodopaminergia). An alcoholic drink in this state will trigger a rush of dopamine in the mesolimbic regions (due to the acute effect of alcohol on the glutamatergic, opioidergic and GABAergic neurotransmission), which can set off states of craving and search for, and consumption of alcohol (Clapp, Bhave, & Hoffman, 2008).

The opioid system and alcohol consumption

The endogenous opioid system is involved in a variety of physiological processes such as analgesia, stress, reward or adaptive homeostatic functions (temperature control, water and food intake). Acute administration of alcohol triggers the release of opioid peptides, which induce positive reinforcing effects and favor the acquisition of self-administrative behavior relating to alcohol.

Both opiate abstinence and opiate administration influence alcohol consumption. High and moderate doses of morphine reduce the preference for alcohol in inverse proportion to the dose taken on the day of injection, On the following day, however, the consumption of alcohol increases (Volpicelli, Ulm, & Hopson, 1991). A small dose of an opioid agonist (like morphine) can act as a primer and induce increased alcohol consumption (Reid & Hunter, 1984). People who have developed heroin dependence tend to drink more alcohol when suffering (heroin) withdrawal; high-dose methadone maintenance, meanwhile, can help them to reduce alcohol consumption (Siegel, 1986).

Ingesting alcohol can also trigger the activation of the opioid system, linked both to the positive reinforcement effect and to loss of control (Reid, 1990). This therefore produces an inverse relationship between the administration of opioid agonists and alcohol consumption, so that even small doses of opiates as well as opiate abstinence prompt an increase in the consumption of alcohol, while high doses of opiates reduce it. This suggests that alcohol and opiates have similar pharmacological effects and that alcohol consumption may be modified by manipulating the endogenous opioid system.

The reinforcing properties of alcohol are modulated (at least in part) by the cerebral opioid receptors. The initial hypotheses were focused on condensation products like acetaldehyde and dopamine, which could induce an increase in ethanol consumption by the direct stimulation of cerebral opioid receptors such as the tetrahydroisoquinolines (Davis & Walsh, 1970), salsolinol (Collins & Bigdeli, 1975) and tetrahydropapaveroline (Greenwald, Fertel, Wong, Schwartz, & Bianchine, 1979). But these hypotheses have been questioned since alkaloids, induced by alcohol consumption, were detected in such small quantities to make it unlikely that they are physiologically active.

The opioid system is of great complexity due to the possible connections between the different peptide agonists, specific opioid receptors and their location in different cerebral areas. Endorphinergic neurons originating in the arcuate hypothalamic nucleus move towards other hypothalamic nuclei of the septum and the accumbens nucleus (important centers mediating the positive reinforcement and reward effects of many addictive drugs) and towards periaqueductal grey matter, amygdala and hypothalamus (Wise & Bozarth, 1982). The proenkephalinergic neurons are widely distributed in the brain, with a greater accumulation in the striatum, periaqueductal grey matter, hypothalamus, periventricular grey matter, hippocampus and raphe nucleus. And the prodynorphinergic neurons are found in the hypothalamus, periventricular nucleus, ce-

rebral cortex, amígdala, hipocampus, periaqueductal grey matter, solitary tract nucleus, spinal medulla, suprarenal and intestinal medulla.

The encephalines (Met- and Leu-encephaline) will link with the delta opioid receptor with an affinity 25 times greater than with the mu opioid receptor. The beta-endorphine recognizes the mu and delta connection points, although a preference for the mu receptor has been described. And the dynorphins interact selectively with the kappa opioid receptor (Gianoulakis, 1993).

In the VTA, opioids would act on the mu receptors, modulating rewarded behaviors. Its activation would result in hyperpolarization of the GABA interneuron, disinhibition of the dopaminergic neuron and increase of the dopamine release in the nucleus accumbens (Johnson & North, 1992), which could favor self-administration and may be related to the craving for alcohol and loss of control.

In the anterior limbic region, the opioids would activate the delta receptors, also triggering an increase in dopamine release in the accumbens nucleus which could be related to the maintenance of self-administration behavior, craving and relapse in people with alcohol dependence (Van Ree, 1987).

In strains of rats selected for their high consumption of ethanol, it has been suggested that this predisposition may be linked to the opioid system since delta opioid antagonists can reduce alcohol consumption (Altshuler, Phillips, & Feinhandler, 1980; Froehlich, Harts, Lumeng, & Li, 1990; Reid, 1990).

Low basal levels of beta-endorphin have been detected in people with risk of alcoholism (having a family record of alcoholism in the three previous generations), compared with people who did not have a family history of alcoholism. Furthermore, the consumption of 0.5 gr/kg of ethanol led to a temporary increase of the plasmatic beta-endorphin in the high risk group (Gianoulakis, Kirshnan, & Thavundayil, 1996). Similarly, alcoholic patients would also exhibit low levels of beta-endorphin after having stopped drinking which would return to normal after 6 months of continued abstention from alcohol (Gennazani, Nappi, Eacchinetti, Mezzella, & Parrini, 1982).

Acute administration of alcohol produces a release of endogenous opioids, especially beta-endorphin, which induces an increase in the release of dopamine in the accumbens nucleus (mediated by the inhibitory action of beta-endorphin on the GABA neurons of the VTA). This increase in dopamine availability may be linked to its positive reinforcing effect, craving and loss of control which can lead to relapse. Therefore, certain pharmaceutical drugs which can act on these neurotransmission systems may modulate the such changes and reduce the risk of relapse (Guardia et al., 2011).

Both mu receptors and delta opioids play a role in reducing alcohol consumption, produced by the antagonists in the opioid receptors. Delta opioids could act in the terminal areas, facilitating dopaminergic transmission; while the mu receptors could indirectly modulate the activity of the dopaminergic neurons, depressing the inhibitory tone applied by the GABA neurons on the dopaminergic neurons in the VTA (Johnson et al., 1992).

On the other hand, a patient with alcohol dependence may exhibit rebound or withdrawal symptoms after not drinking alcohol for several hours, after which a drink or consumption of benzodiazepines may produce a strong negative reinforcing effect since both can rapidly and efficiently neutralize alcohol withdrawal symptoms. Therefore, alcohol can have a double reinforcing effect: a positive one related to the release of endorphins (which will produce disinhibition of mesolimbic dopaminergic neurons) and a negative one linked to its ability to alleviate withdrawal, as well as certain psychiatric symptoms such as anxiety, difficulty falling asleep, phobias, posttraumatic stress or others (Guardia, Surkov, & Cardús, 2010).

The adaptation of kappa receptors to chronic consumption of alcohol

The consumption of alcohol, as with other drugs, triggers dopamine release in the accumbens nucleus, and this forms the neurological background of its reinforcing effect.

The stimulation of mu receptors (possibly caused by the release of beta-endorphin, induced by ethanol) in the VTA (origin of the A10 dopaminergic neurons) produces an increase in dopamine release; meanwhile, the selective blocking of the mu receptor results in a reduction of dopamine release. This is matched by stimulation of kappa receptors, in the interior of the nucleus accumbens, which causes lower dopamine release, while selective blocking triggers a marked rise in dopamine release (Spanagel, Herz, & Shippenbeerg, 1992).

In stressful situations, dynorphine increases in the central nucleus of the amygdala which also co-expresses CRF (corticotropin release factor), and this implies a close relationship between kappa opioid systems and CRF. In addition, dynorphinergic neurons move towards the noradrenergic neurons of the locus coeruleus, a region associated with arousal, attention and the response to stress. Kappa agonists can stimulate the hypothalamic-pituitary-adrenal axis and play a role in the analgesia induced by stress.

In states of drug dependence, inhibition of the kappa receptor can attenuate the compulsive intake of drugs and alcohol, while its activation can induce the restoration of drug or alcohol seeking behavior, generating stress-like symptoms.

The activation of kappa receptors weakens the release of dopamine induced by alcohol consumption and therefore its reinforcing effect, while the intracerebral administration of a kappa receptor antagonist, nor-binaltorphimine,

triggers a reduction of the operant response to ethanol, but only in animals with alcohol dependence. Therefore it appears that chronic consumption of alcohol would produce an increase in the activity of the kappa opioid system, which would be associated with a greater reinforcing effect of alcohol after withdrawal, and this in turn suggests that the drugs which modulate the kappa opioid system may be efficacious in the treatment of alcohol dependence (Shippenberg, Zapata, & Chefer, 2007).

Nalmefene is more efficacious than naltrexone for reducing alcohol consumption in rats with alcohol dependence. Both drugs would have a similar effect on mu receptors, but nalmefene would also have a modulating effect on the kappa opioid receptors and would produce a greater reduction in alcohol consumption than naltrexone in alcohol dependent rats (Keating, 2013; Nealey, Smith, Davis, & Walker, 2011; Walker & Koob, 2008).

Both the activation as well as the hyperfunction of kappa opioid receptors result in a reduction in the release of dopamine, in both the limbic system and the prefrontal cortex, generating a state of hypodopaminergia and hyperglutamatergia which runs parallel to a negative emotional state during abstention from alcohol and contributes to a greater negative reinforcing effect of a new alcoholic drink. This hypodopaminergia in the prefrontal cortex may furthermore contribute to more impulsive decision making, less cognitive control of addictive behavior and a certain impairment of the executive functions. The kappa receptor antagonists reduce the self-administration of alcohol in rats which have developed alcohol dependence and exhibit hyperfunction of the dynorphin/kappa system (Sirohi, Bakalkin, & Walker, 2012).

The alcohol deprivation effect

After a two-day period of deprivation, monkeys which self-administer alcohol increase their consumption. The longer the deprivation period, the greater the increase in alcohol consumption. Kornet, Goosen and Van Ree (1990) called this the "catch up" or "making up for lost time" phenomenon. It can be reverted by administering naltrexone (Kornet, Goosen, & Van Ree, 1991).

It is a phenomenon similar to that exhibited by alcoholic patients who stop drinking for a period. On the day they try an alcoholic drink again, they have greater problems than before to control consumption, and this effect can be neutralized by previously taking naltrexone or nalmefene (O'Brien, Volpicelli, & Volpicelli, 1996).

The neurological foundation of the deprivation effect is the powerful release of dopamine which takes place in the accumbens nucleus and other limbic structures in a brain which has adapted to alcohol, and which has a weakened dopaminergic tone (hypodopaminergia). Renewed alcohol consumption will produce a release of endogenous opioids, disinhibition of dopaminergic neurons and a significant increase in craving and loss of control regarding alcohol consumption (Clapp et al., 2008; Johnson et al., 1992). This is therefore not only a psychological effect, but also a neurobiological phenomenon which only takes place in people who are alcohol dependent and which can be attenuated or neutralized by opioid receptor antagonists.

Opioid Receptor Antagonists and Reduced Alcohol Consumption

The opioid system would act as a mediator of the reinforcing effects of alcohol which lead to drinking excessively. Naltrexone and nalmefene, which block the opioid receptors, would prevent an increase of in the activity of the opioid system after ingesting alcohol and this effect would be of decisive relevance for alcoholic patients who have a drink after a period of abstention. By reducing the reinforcing strength of alcohol in these circumstances, the risk of relapse into excessive alcohol consumption would be reduced (Guardia Serecigni, 2011).

Preclinical studies with animals

Studies with animals have shown that alcohol triggers an increase in beta-endorphin release in the pituitary (Seizinger, Holtz, & Herz, 1984), especially in rats who "prefer" alcohol in contrast to control rats (Froehlich, Zweifel, Harts, Lumeng, & Li, 1991). This preference, genetically determined and related to the the endorphinergic system, seems to be confirmed with respect to the sensitivity of the encephalinergic system to alcohol (Li, Li & Froehlic, 1992). In persons with a risk of alcoholism, consumption of alcohol can also trigger an increase in the β-endorphin in plasma (Gianoulakis et al., 1996).

The preference of Naltrexone for the mu receptor is elevated, medium for kappa and low for delta. The preferred ligands of the mu receptor are beta-endorphin and enkephalin, those of the delta receptor are the leu- and met-enkephalines, and dynorphins A and B are those preferred by kappa receptors. Therefore, although beta-endorphin is not a selective ligand, it has considerable affinity for the delta receptor (Terenius, 1996). Nalmefene has a greater modulation spectrum of the opioid receptors, being mu and delta receptor antagonist and partial agonist of kappa receptors (Keating, 2013; Nealey et al., 2011; Sirohi et al., 2012; Walker et al., 2008).

Laboratory trials with humans

In laboratory trials carried out in experimental bars with people exhibiting excessive alcohol consumption and who had not sought treatment for alcoholism, naltrexone achieved a reduction in the positive reinforcing effect of alcohol, the compulsion to drink, the number of units consumed, the speed of alcohol consumption and a possi-

ble increase in undesirable effects of alcohol intoxication, such as cephalea or nausea, compared to placebo (Davidson, Palfai, Bird, & Swift, 1999). In other words, people who took naltrexone noticed that alcoholic drinks did not have the same reinforcing effect on them (they said that it did not taste as good as before), that they drank more slowly (their drinks lasted longer), and the total number of drinks per session was lower. After several alcoholic beverages, they changed to non-alcoholic drinks and some said they felt more drunk than was normal for them, or had some unpleasant symptoms.

Both naltrexone (50 mg/day) and nalmefene (40 mg/day), managed to reduce the craving for more after the first alcoholic drink, the number of drinks consumed, the choice of an alcoholic drink when non-alcoholic alternatives were available, and the euphoria-inducing effect of alcohol (Drobes, Anton, Thomas, & Voronin, 2004).

Clinical trials on treatment of alcoholism

When alcoholic patients manage to reduce alcohol consumption, or to stop drinking for a period, they tend to recover rapidly from the consequences of alcohol, but the conditioned stimuli can again trigger a craving which leads to more alcohol consumption, after which the difficulties to control drinking and even the loss of control reappear, which can lead to relapse. Although some people manage to stop drinking without any help for long periods, others need specialized treatment to reduce their tendency to relapse (Work Group on Substance Use Disorders, 2007).

The neurobiological background of alcohol dependence are the persistent neuroadaptive changes induced by excessive and continued use of alcohol. Clinical manifestations are heightened tolerance, sensitization, craving, alcohol dependence and abstinence. Dependence is defined as the need to continue taking a substance to prevent withdrawal symptoms, but the traditional differentiation between physical and psychological dependence is artificial given that both are involved in the dysfunction of certain structures in the central nervous system (Guardia et al., 2010; Nestler, Hope, & Widnell, 1993).

Opioid receptor antagonists such as naltrexone and nalmefene reduce alcohol consumption in both animals (Froehlic & Li, 1993) and in social drinkers in an experimental bar situation (Davidson et al., 1999; Drobes et al., 2004), as well as in recovering alcoholic patients. This makes them very useful in the prevention of relapse (Anton et al., 2006; Guardia, Caso, Arias, Gual, Sanahuja et al., 2002; O'Malley, Jaffe, Chang, Scottenfeld, Meyer et al., 1992; Volpicelli, Alterman, Hayashida, & O'Brien, 1992).

Controlled clinical trials on the treatment of alcoholism have proven that opioid receptor antagonists trigger a reduction in the reinforcement or euphoria-inducing effects of alcohol consumption, a reduction in craving, improved control after a first drink or even a certain aversive effect on alcohol consumption (Swift, Whelihan, Kuznetson, Buongiorno, & Hsuing, 1994; Volpicelli, Watson, King, Sherman, & O'Brien, 1995).

The expected effect is, therefore, to improve the patient's self-control with regard to alcohol consumption and in the long term even eliminate the addictive conditioning, allowing the patient to progressively recover his/her freedom in decision-making and mitigating his/her obsession with drink (Guardia Serecigni, 2011).

The COMBINE study, carried out in USA (Anton et al., 2006), compares different modalities of pharmacological and psycho-social treatment of alcoholism, and concludes that one of the most useful indicators for evaluating the results of treatment is the number of heavy drinking days because this correlates well with the number of negative consequences that the patient suffers during the treatment as a consequence of excessive alcohol consumption (Falk, Wang, Liu, Fertig, Mattson et al., 2010). This correlation suggests that if patients manage to have fewer than 5 (men) or 4 (women) drinks per day, they would not suffer any, or just a few negative consequences, just like people who have stopped drinking. That is to say, the odd low-risk drink would have the same favorable results as complete and continued abstinence.

In other words, not drinking every day and remaining below heavy drinking limits at every sitting could be considered clinical remission since this behavior would not be associated with negative consequences. Therefore, treatment aimed at reducing alcohol consumption can be as satisfactory as continued abstinence, provided the patient does not exceed the limits of low-risk consumption at any sitting.

In the COMBINE study, naltrexone oral in 100mg/day doses for 16 weeks achieves a rise in the days of abstention (80.6% vs. 75.1%) and a reduction of the risk of excessive drinking (66.2% vs. 73.1%) compared to placebo. In addition, a criterion called "good clinical result" was used, defined by the authors as no more than 2 heavy drinking days per week, a maximum of 14 units per week for men (11 for women) and the absence of significant problems linked to alcohol during the last 8 weeks of the 16-week treatment (Anton et al., 2006; Anton, 2008).

Those patients who drank during the COMBINE study exhibited less serious symptoms and greater likelihood of achieving a personal target of controlled consumption. Furthermore, in various studies the therapeutic effect of naltrexone did not become statistically significant until the second month of treatment (Anton et al., 2006; Bouza, Magro, Muñoz, & Amate, 2004; Guardia et al., 2002), which suggests that its effect may be progressive and would not clearly manifest itself until the patient had a first alcoholic drink.

As with naltrexone, the first clinical trials with nalmefene were focused on achieving abstention from alcohol, but revealed some advantages over naltrexone such as, for example, not having a dose dependent risk of hepatic toxicity, higher bioavailability, and its opioid receptor antagonist effect being more competitive and lasting longer. Taken daily, nalmefene proved to be efficacious in preventing relapses into excessive alcohol consumption in the majority of studies (Karhuvaara, Simojoki, Virta, Rosberg, Loyttiniemi et al., 2007; Mason, Ritvo, Morgan, Salvato, Goldberg et al., 1994; Mason, Salvato, Williams, Ritvo, & Cutler, 1999), but not better than placebo in the study reported by Anton, Pettinati, Zweben, Kranzler, Johnson et al. (2004).

Following this, the study by Karhuvaara et al. (2007) led to a new procedure called targeted nalmefene, in which people with excessive alcohol consumption were instructed to take the drug when they felt that they were about to drink alcohol. With simple medical management this procedure achieved a significant reduction of excessive alcohol consumption in comparison with placebo. Another study of targeted nalmefene concluded that polymorphic variations in the genes of opioid receptors do not modify the response to treatment with nalmefene, in contrast to what happens in the treatment with naltrexone, where ASN40ASP polymorphism of the mu OPRM1 receptor affects the response to naltrexone treatment (Arias, Armeli, Glernter, Covault, Kallio et al., 2008)

The Pharmacology of Naltrexone and Nalmefene

Trials carried out with naltrexone have confirmed its **efficacy** in reducing alcohol consumption and relapse rate at the end of three months of treatment for alcoholism (Anton et al., 2006; Bouza et al., 2004; Pettinati, O'Brien, Rabinowitz, Wortman, Oslin et al., 2006; Srisurapanont & Jarusuraisin, 2005). Cochrane's meta-analyses have confirmed that naltrexone (50mg/day for 12 weeks) achieves a 36% reduction in the relapse rate and reduces the number of days of alcohol consumption, excessive drinking, total consumption of alcohol, craving, and also the levels of gamma-glutamyltransferase. Nevertheless, the effect size has been considered small to moderate (Kranzler, Modesto-Lowe, & Van Kirk, 2000; Rösner, Hackl-Herrweth, Leucht, Vecchi, Srisurapanant et al., 2010).

In some controlled trials, naltrexone has not proved to be better than placebo in terms of preventing relapse (Gueorguieva, Wu, Pittman, Cramer, Rosenheck et al., 2007; Krystal, Cramer, Krol, Kirk, & Rosenheck, 2001; Oslin, Lynch, Pettinati, Kampmann, Gariti et al., 2008;). However, a reanalysis of two negative studies suggests that naltrexone can reduce the risk of excessive consumption and raise the likelihood of abstention (Chick, Anton, Checinski, Croop, Drummond et al., 2000).

Adhering to the medication regimen can be decisive if the reduction in the relapse rate or craving are to reach statistical significance compared to placebo (Anton, 2008). It is therefore possible that the efficacy of naltrexone increases if administration is supervised by a relative or nurse, in which case the patient can also be intensively monitored and urine tests carried out periodically (Guardia Serecigni et al., 2008).

Extended-release injectable naltrexone is adminstered in 380mg doses every four weeks and produces a reduction in heavy drinking days of 25%, and in the alcohol consumed on the days the patient drinks again. The onset of the therapeutic effect may be very fast (from the second day onwards) and may be sustained throughout the treatment, which means that the patient's commitment to the treatment and specialized psychotherapeutic intervention may be more easily maintained (Ciraulo, Dong, Silverman, Gastfried, & Pettinati, 2008; Garbutt, Kranzler, O'Malley, Gastfriend, Pettinati et al., 2005). A study carried out with 624 patients has shown that extended-release naltrexone did not have hepatotoxic effects, not even among patients who continued heavy drinking during the treatment, and achieved a reduction in GGT better than placebo in weeks 4, 8, 12 and 20 of the treatment (Lucey, Silverman, Illeperuma, & O'Brien, 2008).

Pharmacokinetics and Pharmacodynamics

Naltrexone is a cyclopropyl derivative of oxymorphone, structurally similar to naloxone and nalorphine. Taken orally, it is rapidly and almost completely (95%) absorbed. It reaches peak concentration after one hour and circulates 21% bound to plasma proteins. It has a half life of 3.9 hours (reaching 9.7 hours after chronic administration), its levels decline during the first 24 hours. It undergoes intense first-pass hepatic metabolism through the cytosol system, mediated by the 3 hydrodiol-dehydrogenase. Approximately 95% of the naltrexone absorbed is metabolized and converted in its principal active metabolite, 6-beta-naltrexol, a pure opioid antagonist with a longer half life than naltrexone (12.9 hours), which facilitates its longer lasting action. It is mainly eliminated by the kidneys. Equilibrium is quickly established and the drug does not accumulate.

It is believed that naltrexone acts as a competitive antagonist of the mu, delta and kappa opioid receptors, with a greater affinity for the mu receptor (Ortiz Camúñez, 1996). A 50 mg administration blocks the opioid receptors for 24 hours. Long-term studies (21 months) show that tolerance for naltrexone opioid antagonist properties does not appear to develop (González & Brogden, 1988).

Nalmefene has a partial agonist effect on the kappa opioid receptors, but with a kappa receptor system in up-regulation as a result of chronic drinking it acts as a functional antagonist (Keating, 2013; Kisler, Sirohhi, Reis, Jansen,

Quock et al., 2013). This receptor profile of nalmefene has been linked to its superior efficacy over naltrexone for reducing alcohol consumption in rats with alcohol dependence (Walker et al., 2008).

The recommended therapeutic dose is 50 mg per day for naltrexone and 18 mg/day for nalmefene. In the first few days of treatment it may be advisable to administer only 25 mg/day to reduce the possible adverse effects of naltrexone. However, in the COMBINE study, as well as some other studies carried out the USA, doses of 100 mg/day for 16 weeks of treatment were used (Anton et al., 2006; Anton, 2008).

Nalmefene has a methylene radical (C=CH2) substituted by a ketonic group (C=O) in position 6 with respect to naltrexone, and in comparison with naltrexone it has greater bioavailability (40-50%), a longer half life and greater affinity for delta and kappa opioid receptors.

Nalmefene is absorbed rapidly, reaches peak plasmatic concentration after 2-3 hours and does not modify the ECG QTc interval, nor the T-wave morphology. It does not, therefore, disrupt cardiac rhythm, nor require QTc monitoring in clinical practice (Matz, Graff, Vainio, Kaillio, Hojer et al., 2011). It has a half life of 13.4 hours and linear pharmacokinetics. After two hours, mu receptor occupation is 93%-100% and is kept at a high level for longer than 24 hours, at the same time as its plasmatic concentration diminishes progressively, which suggests a slow dissociation of the mu opioid receptor. Its prolonged occupation of mu opioid receptor after isolated or repeated administration makes it very suitable for non-daily administration (Ingman, Hagelberg, Aalato, Nagren, Juhakoski et al., 2005; Niciu & Arias, 2013).

It is held that nalmefene metabolites do not contribute significantly to its pharmacological effect. Nalmefene is extensively and rapidly metabolized by glucuronide conjugation and is eliminated by the kidneys. While naltrexone is metabolized oxidatively, nalmefene metabolizes primarily by glucuronide conjugation and does not display dose dependent hepatotoxicity, which improves its safety profile for patients with hepatic dysfunction (Salvato & Mason, 1994; Niciu & Arias, 2013).

The side effects of naltrexone may affect 30% percent of patients, with nausea and cephalea being the most frequent, followed by dizziness, vomiting, stomach pain or discomfort, anorexia, asthenia, agitation, insomnia or anxiety. These can appear in the initial days of treatment, are usually of low intensity and tend to disappear (Croop, Faulkner, & Labriola, 1997). Starting treatment with a lower dose (25 mg/day) and accompanied by a meal can minimize adverse effects and favor progressive adaptation of the organism. Over the following days, the dose is raised to the normal level of 50 mg/day.

Of the possible adverse effects of nalmefene, the most frequent are dizziness, nauseas and sleep disorder. Other less frequent symptoms are dry mouth, cephalea, tachycardia/palpitations, sweating, muscle spasms, anorexia, weight loss, asthenia. Most of them are light or moderate, appear at the beginning of the treatment and are short-lived. Exceptional cases of confusion, hallucination and dissociative symptoms have been reported. Most of the side effects tend to diminish without the need to modify treatment and do not reappear with new administration.

Nalmefene does not modify the ECG QTc interval, nor the T-wave morphology (Keating, 2013) and during treatment in the ESENSE trials no clinically relevant changes or differences between nalmefene and placebo took place with regard to vital signs, laboratory analysis, body weight, electrocardiographic registers and scores on the Profile Mood States scale which assesses possible emotional symptoms (Gual, He, Torup, van den Brink, & Mann, 2013; Keating, 2013; Mann, Bladstrom, Torup, Gual, & van den Brink, 2013).

Tolerability and Safety

At doses of 50 mg/day, naltrexone is a well-tolerated drug with few adverse effects, especially when the patient does not drink alcoholic beverages excessively. Alcoholic patients treated with naltrexone for 12 weeks tend to show an improvement in their hepatic enzymes. Possible side effects tend to diminish within 7 to 14 days and can be minimized by starting the treatment with 25 mg/day during the first week.

Instead of an increase, naltrexone triggers a decrease of certain hepatic enzymes such as gamma-glutamyltransferase (GGT) and aspartate-aminotransferase (AST). While in the control group GGT is also reduced, this is not the case with AST. At the end of the treatment, no significant differences were detected in terms of GGT and AST levels between the experimental and control groups when comparing with basal levels of these hepatic enzymes (Croop et al., 1997; Guardia et al., 2002; O'Brien et al., 1996). In a pilot study carried out with obese patients who received doses six time higher than normal (300 mg/day), elevated transaminase was detected, due to hepatocellular damage, but this receded when naltrexone was stopped.

The ESENSE trials have shown that the treatment with nalmefene is associated with a reduction of the hepatic enzymes alanine-aminotransferase (ALT) and gamma-glutamyltransferase (GGT), significantly greater than in patients taking the placebo (Mann et al., 2013; Gual et al., 2013).

Indications and Contraindications

Before prescribing naltrexone or nalmefene, it is advisable to rule out consumption of opiates since both drugs antagonize their possible therapeutic effects and would trigger serious withdrawal symptoms in people who have de-

veloped opiate dependence. And should the patient need surgical intervention he/she would have to stop taking naltrexone or nalmefene 3-7 days before the intervention, particularly in the case of major surgery (Anton, 2008).

It is advisable to take into account the patient's hepatopathy background and associated drugs with hepatotoxic potential. In the analyses prior to starting treatment, patients should be asked for indicators of hepatic and renal function, complete hemogram, pregnancy test (women of fertile age) and urine tests for the presence of opiates and other substances.

Due to its posible hepatotoxic effect, naltrexone is contraindicated in pregnancy, lactation, acute hepatitis, hepatic insufficiency, hepatocellular damage, recent consumption of opiates, active dependence on heroin or other opiates, withdrawal symptoms from opiates, acute withdrawal from alcohol and patients who need opioid analgesics, antitussives or antidiarrheals (González et al., 1988; Ortiz Camuñez, 1996). In patients with acute hepatitis, liver failure or serious hepatocellular problems, reflected in elevated hepatic enzymes at three times the normal limit and/or the bilirrubinemia, precautions need to be taken if the patient is suffering from a less serious hepatic dysfunction or have a recent history of hepatopathy (Berg, Pettinati, & Volpicelly, 1996).

Nalmefene is contraindicated in pregnancy, lactation, serious deterioration of hepatic or renal function, recent consumption of opiates, dependence on heroin or other opiates, withdrawal symptoms from opiates, acute withdrawal from alcohol, patients who need opioid analgesics, antitussives or antidiarrheals (Keating, 2013; European Medicines Agency, 2013).

Nalmefene treatment should be interrupted one week before surgical interventions which could require the administration of opioid analgesics. Care is advised when treating patients with transaminases (ASAT and ALAT) more than 3 times above the normal limit, and hepatic and renal function should be monitored in patients with deteriorated liver or kidney function. Given that the results of trials with animals show potential reproductive toxicity, it is not advised to take nalmefene during pregnancy or the lactation period since the drug is excreted through milk. Nevertheless, the possible advantages of the treatment should be considered if the patient has had a favorable prior experience with nalmefene and suffers from excessive alcohol consumption during lactation.

Possible interactions

Naltrexone presents a low level of interaction due to its hepatic metabolism by the cytosolic and not the cytochrome P450 system. Some authors consider that it could be administered with disulfiram and other psychotropic medication, at usual doses, taking care to monitor hepatic function periodically (Berg et al., 1996).

Nalmefene is metabolized by CYP450 and UGT enzymes. Long-term treatment alongside powerful inhibitors of enzyme UGT2B7 (such as diclofenac, fluconazole, medroxyprogesterone or meclofenamic acid) may increase the exposure to nalmefene. On the other hand, simultaneous treatment with UGT enzyme inductors (such as dexametasone, phenobarbital, rifampicin and omeprazol) may diminish the efficacy of nalmefene due to reduced plasma concentrations.

Both naltrexone and nalmefene block the analgesic, antitussive or antidiarrheal effects of opioid drugs prescribed to these ends and can trigger serious opiate withdrawal symptoms in people actively dependent on heroin, methadone, buprenorphin or other opiates.

There is no clinically significant pharmacokinetic interaction between nalmefene and alcohol, which means that nalmefene neither raises nor lowers alcohol intoxication.

Differential characteristics of nalmefene

Nalmefene has been considered a modulator of the opioid system. It acts as an antagonist of the mu and delta receptors (opioids), and partial agonist of the kappa receptors, but some author propose that in up-regulation of the kappa receptors it could act as antagonist (Keating, 2013). Compared to naltrexone, it has greater affinity for delta and kappa receptors, greater bioavailability, a longer half life and, therefore, a longer-lasting effect. Moreover, no indications have been found of dose-dependent hepatotoxicity (Nutt, 2014).

Some authors claim that, given its differential effect on the kappa opioid receptors, nalmefene is more efficacious than naltrexone in reducing alcohol consumption when the organism has developed a dependence on alcohol (Walker et al., 2008; Walker, Zorrilla, & Koob, 2011). Chronic alcohol ingestion leads to an up-regulation of the dynorphin/kappa opioid system in the person who has developed alcohol dependence, which would be associated with a state of hypodopaminergia linked to higher levels of craving. Nalmefene could renormalize such a state of hypodopaminergia and, therefore, reduce craving for alcohol (Spanagel & Vengeliene, 2012).

With regard to the aim of continued abstention, nalmefene has proven efficacious in preventing relapses in some clinical trials (Mason et al., 1994; 1999), although in one case this could not be confirmed (Anton et al., 2004). In terms of the new objective of reducing alcohol intake, some pilot studies signalled that naltrexone and nalmefene could be of use since they would result in a reduction of the number of days in which a person drank alcohol, the number of drinks per sitting, the number of heavy drinking days and the numbers for the biological markers ALT and GGT (Heinala, Alho, Kiianmaa, Lonquist, & Sinclair, 2001; Hernández–Avila, Song, Kou, Tennen, Armeli et al., 2006; Kranzler, Tennen, Armeli, Chan, Covault et al., 2009).

The efficacy of nalmefene in connection with the new treatment target of alcohol intake reduction has been assessed on the basis of three placebo controlled multicenter studies in Europe, with a new procedure in which the alcoholic patient takes an 18 mg pill of nalmefene only on the day in which alcohol consumption is likely or when facing a situation with a risk of relapse.

Based on the results of the ESENSE 1 and 2 studies (Gual et al., 2013; Mann et al., 2013), the indication of nalmefene for reducing alcohol consumption in alcohol dependent persons has been confirmed, and the European Medicines Agency approved this new indication in 2013.

A New Target in the Treatment of Alcoholism

Treatment with nalmefene leads to a reduction in alcohol consumption. Not drinking alcohol every day and drinking less per sitting is a realistic objective for low-risk alcoholic patients if they take nalmefene, above all if they are motivated and committed to cutting down their alcohol intake.

Therefore, people with difficulty in controlling alcohol consumption, those who have already suffered some of the negative consequences and recognize the need to reduce their alcohol intake, can benefit from the treatment with nalmefene.

The profile of the ideal patient would probably be of a middle-aged person with mild alcohol dependence, who does not have clear withdrawal symptoms, who has applied for alcoholism treatment for the first time, who does not have serious medical, psychiatric or addictive comorbidity, and who is determined to cut down substantially on his/her alcohol consumption. A stable family, social and work environment, furthermore, will favor the results of the treatment (Van Amsterdam & Van den Brink, 2013).

Excessive alcohol consumption tends to be associated with negative consequences. The majority of those who suffer such negative consequences do not have an alcohol consumption disorder. They can be said to have such a habit but are capable of modifying it when they wish to because they have not yet developed an addiction. They can, therefore, reduce their intake when they seriously decide to do so, without needing specialized treatment.

When a person has developed alcohol addiction it is unlikely that he/she will be able to reduce consumption and effectively maintain it at low levels for a prolonged period of time. The cardinal symptom of alcoholism is precisely the difficulty in controlling alcohol intake, above all the first drink, and the opioid receptor antagonists would neutralize this symptom. The effort to reduce alcohol intake is a necessary but insufficient condition; nalmefene helps the person who is determined to reduce drinking to achieve his/her aim.

Alcoholism treatment with nalmefene achieves something similar to the medical model of treatment in which a specific drug neutralizes a specific symptom. In people suffering from alcoholism, the symptom is behavioral, the difficulty to control or the loss of control.

Nalmefene for reducing alcohol consumption

The ESENSE trials were carried out on patients with mild or moderate alcohol dependence disorder, that is without alcohol withdrawal symptoms (which did not exceed 10 points on the CIWA scale), and without serious medical, psychiatric or addictive comorbidity. These were patients, then, who did not need alcohol detoxification treatment and who could begin nalmefene treatment as outpatients and without having to stop drinking.

In each visit, the motivational and psychoeducational intervention procedure was applied to enhance adherence to the treatment. This procedure is known as BRENDA, an acronym representing the six successive actions which can be carried out on each patient visit: a biopsychosocial evaluation is first carried out, a report of the biopsychosocial evaluation is presented to the patient, empathy with the patient and his/her response to the report is necessary, the needs of the patient are identified, direct advice is given to the patient regarding attainment of treatment targets, an assessment of the patient's response to the clinician is prepared and the clinician adapts to the patient's preferences in order to reach final consensus on future goals (Volpicelli, Pettinati, McLellan, & O'Brien, 2001).

With the aim of introducing the new procedure "as needed", the patient is instructed to take a 20 mg nalmefene pill only on those days when he/she intends to have an alcoholic drink or in situations in which it is likely he/she will have an alcoholic drink, in which case it is recommended that, if possible, the pill be taken one hour before the first alcoholic drink or if not, as soon as possible, even together with the first alcoholic drink.

Patients on the ESENSE program took nalmefene (or placebo) for six months in a randomized, double blind manner. The ESENSE 1 study took place in northern European countries, while ESENSE 2 was carried out in southern Europe. The treatment goal was to achieve change from the beginning to month 6 in the number of heavy drinking days and the average of total alcohol consumption per session. Patients who were given the active ingredient took it on 48% and 57% of the days, while those who were assigned the placebo did so on 63.9% and 65.2% of the days in ESENSE 1 and 2 respectively.

Between the selection and randomization interviews, a high percentage of patients (18% in ESENSE 1 and 33% in ESENSE 2) had already reduced their alcohol consumption to below 6 heavy drinking days during the 4 previous weeks, or to below the average level of risk of drinking,

which were the criteria for inclusion in the study and which had been confirmed in the selection interview.

In the next step in the procedure, nalmefene resulted in a reduction in the number of heavy drinking days significantly greater than placebo in both ESENSE studies, as well as a reduction of total alcohol consumption in ESENSE 1 but not in ESENSE 2.

The concept RESPONSE to the treatment was defined as a reduction from a very high level of risk of alcohol consumption to a mid- or low level, or from high or mid-level risk to low-level risk. Logically, patients who managed a significant reduction in alcohol intake between the selection visit and the beginning of treatment could not reduce their consumption further during the course of treatment, that is they began the treatment with a low level of risk and maintained this level throughout. Nevertheless, a subanalysis of the group of patients who at the start of treatment still had high risk consumption (>60 gr/day for men, >40 gr/day for women) confirmed nalmefene's efficacy in reducing consumption, with significantly better results in comparison with placebo.

Moreover, those taking nalmefene exhibited a greater reduction in their scores on the global clinical impression scales, both those for severity and for improvement, and also in the ALT and GGT levels, with significant differences in favor of nalmefene.

In a third study, called SENSE, in which treatment lasted for 12 months, the same procedure was followed to assess the safety, tolerability and efficacy of nalmefene in patients with alcohol dependence. A substantial reduction of alcohol intake between the selection interview and beginning of treatment was achieved by 39% of patients. Retention after 12 months was 63% and the reduction, both in terms of heavy drinking days and total alcohol consumption, was significantly higher with nalmefene than placebo after 12 months of treatment, as were the reduction of scores on the global clinical impression scales (severity and improvement) and in ALT and GGT levels (Van den Brink, Aubin, Bladström, Torup, Gual et al., 2013; Van den Brink, Sorensen, Torup, Mann, & Gual, 2014).

An analysis of the subgroup of those who continued high-risk consumption at the start of the nalmefene treatment confirmed a satisfactory response in 72% of those who took nalmefene, in contrast to 57% who took the placebo by the end of the treatment.

Nalmefene was well-tolerated and the adverse effects which appeared most frequently (>5%) were dizziness, nausea, cephalea, insomnia, vomiting, fatigue and loss of appetite. Other less frequent symptoms were hyperhidrosis, somnolence, tachycardia, nasopharyngitis and sleep disorder.

The adverse effects appeared from the first day of treatment with nalmefene, the majority were transitory (3-7 days) and of light to moderate severity (Van den Brink et al., 2013; 2014). Those which led most frequently to abandonment of treatment were dizziness, nausea, fatigue and cephalea. Comparing the serious side effects which appeared in patients taking nalmefene or placebo produced the following figures respectively, 5.9% vs. 6.7% in the ESENSE 1 study, 2.2% vs. 4.7% in ESENSE 2 and 6.9% vs. 5,4% in the SENSE study. This suggests that the majority of adverse effects were not attributable to nalmefene but rather to the patients' own pathology since patients did not stop drinking during the nalmefene treatment and also because the procedure for data collection means that any symptom that the patient mentions in any of the visits is registered as a possible side effect, irrespective of whether or not it can be attributed to the drug (Keating, 2013).

A state of confusion, or hallucinatory or dissociative symptoms appeared only exceptionally and only at the beginning of the treatment, were of light or moderate severity and short-lived, and did not reappear when nalmefene administration was repeated (European Medicines Agency, 2013).

Advantages of nalmefene treatment to reduce alcohol consumption

Treatment with nalmefene is safe, well-tolerated and simple. It leads to a reduction in heavy drinking days and the amount of alcohol consumed per session in patients with alcohol dependence (Gual et al., 2013; Mann et al., 2013).

Lower alcohol consumption is associated with a reduction in the number of accidents, hostile or self-destructive behavior and heart rhythm disorders (Rehm, Baulinas, Borges, Graham, Irving et al., 2012). The COMBINE study detected a reduction in negative consequences parallel to lower alcohol intake, to the extent that those patients who did not have a single day of excessive consumption also avoided the negative consequences normally associated with it (Anton et al., 2006; Falk et al., 2010).

In comparison to continued abstinence, the target of reduced intake has the advantage of adapting better to the need for help of the alcoholic patient. Patients frequently state that they wish to stop drinking, but equally often, they hope that at some point in the future they can have an alcoholic drink. In other words, patients' expectation, and often that of their families, is that after a period of abstention the problem will have been resolved and that they will have recovered control over their drinking; the belief that control is voluntary and depends exclusively on the patient's willpower to succeed is widespread.

In reality, unfortunately, due to the deprivation effect, the day they try an alcoholic drink again after a period of abstention, it is most likely that they will lose control over their drinking.

Moreover, patients who hope to be able to enjoy a drink at some time in the future without the risk of problems will

not accept the goal of complete and continued abstention, and will reject medication which prevents them from having the odd drink. Some patients will refuse treatment for alcoholism if they have to stop drinking entirely.

The treatment with nalmefene aimed at reducing alcohol intake adapts better to the needs of a majority of patients beginning treatment for alcoholism. It may favor the acceptance of, adherence to, and retention in the treatment program, as well as the commitment to the new goal of reducing alcohol consumption.

For patients it might be difficult to understand: (1) controlling alcohol consumption is a function of the nervous system and is not governed by the patient's willpower; (2) this control depends on the proper functioning of certain brain structures; (3) intervening in the opioid receptors can result in a normalization of control over alcohol consumption; (4) one simple pill can achieve this. The COMBINE study has shown that both naltrexone (100 mg/day) and cognitive behavioral therapy achieve greater efficacy than placebo. However, the combination of both does not achieve better results than naltrexone accompanied by simple medical management, that is in order to attain the greatest therapeutic benefit with naltrexone, it is not necessary to apply psychological treatment (Anton et al., 2006).

In the ESENSE studies with nalmefene, a small motivational intervention known as BRENDA was employed to optimize management and adherence to the medication (Volpicelli et al., 2001). Any motivational intervention aimed at reducing alcohol consumption and keeping to the program can therefore be helpful in terms of optimizing the efficacy of nalmefene.

It is advisable to carry out a good analysis of the alcohol consumption patterns of the patient, give him/her clear and simple instructions and recommendations (both verbal and written) about the reduction of alcohol and managing nalmefene, and monitor the patient to support ongoing learning about the new therapeutic procedure, helping him/her to overcome potential hurdles and circumstances that may appear during the course of treatment.

The active participation of the alcoholic patient, in the initial decision as to the goal of the therapy and the individualized management of it, improves adherence to the therapy and retention in the treatment program. It is the patients themselves who decide when the medication is taken and even when alcohol can or cannot be drunk. It adapts better to the patients' own objectives and prevents an occasional drink turning into relapse, helping patients to successfully overcome situations with risk of relapse. If the patients do not consider an occasional drink as a relapse, that is if they do not feel as if they have relapsed, it is less likely that they will abandon the treatment program. Remaining on the program furthers doctor-patient rapport, offering more opportunities to become aware of problems, progressively changing attitudes with respect to alcohol consumption, and progressively reducing the tendency to drink heavily.

Among the advantages of treatment with nalmefene we can highlight (1) patients being well-disposed to the treatment, probably due to their greater participation and implication in decision-making. (2) A more specific effect on the "difficulty of control" symptom which facilitates the understanding of the way nalmefene works, both for the patients as well as their families. (3) An increase in the likelihood that patients will request treatment, and at an earlier stage in their illness. (4) The possibility, in this case, of halting the development of the illness in its initial stages, thereby preventing the increase and progressive worsening of the negative consequences of excessive alcohol consumption that both patients and their families would have suffered in the future. (5) The treatment with nalmefene is safe, well-tolerated, simple, and does not require psychotherapy, just the instructions of a medical expert.

On each visit during the course of treatment with nalmefene, an analysis can be made of the factors which increase the risk of loss of control over drinking and work on coping strategies to make sure that the patient keeps to low-risk levels of consumption. At the same time, it is possible to consolidate the parallel psychiatric comorbidity diagnosis (anxiety, affective or personality disorders) and detect possible concomitant consumption of other drugs or medicines of abuse, which can interfere with the recovery from alcoholism. These data enrich the understanding and personalized diagnosis of each alcoholic patient and permit the optimization of each patient's development.

If the patient is motivated to take the treatment, it is more likely that he/she will be willing to change attitudes, behavior, lifestyle, etc., essential for making progress in his/her recovery. If there is a bout of heavy drinking during the course of treatment with nalmefene, the patient is more likely to ask for help and, if a good analysis is made of the relapse, the patient is more likely to accept a new plan of treatment which he/she may have rejected at the start of the treatment, given that he/she had not yet become aware of the severity of the problem.

Finally, it is important to bear in mind that nalmefene is the only medication which has been approved by the health authorities for use in reducing alcohol consumption in patients with alcohol dependence.

Conclusions

1. Opioid receptor antagonist drugs (nalmefene and naltrexone) lead to a reduction in alcohol consumption
2. Opioid receptor antagonists can prevent an occasional alcoholic drink from turning into a relapse because they can attenuate the deprivation effect.

3. Both naltrexone and nalmefene manage to reduce craving after a first alcoholic drink, the amount of alcohol drunk per sitting, the choice of alcoholic drinks over non-alcoholic drinks, and the euphoria-inducing effect of alcohol.
4. The treatment target of reducing alcohol consumption can obtain the same results as continued abstention, as long as the patient does not exceed the limits of low-risk consumption at each sitting.
5. Nalmefene may be more effective than naltrexone in reducing alcohol consumption in people with alcoholism thanks to its modulating effects on the kappa opioid receptors.
6. Nalmefene helps the person who decides to reduce his/her consumption to achieve this goal.
7. The profile of the ideal patient would probably be of a middle-aged person with mild alcohol dependence, who does not have clear withdrawal symptoms, who has applied for alcoholism treatment for the first time, who does not have serious medical, psychiatric or addictive comorbidity, and who is determined to cut down substantially on his/her alcohol consumption.
8. Among the advantages of treatment with nalmefene it is worth highlighting that it is safe, well-tolerated, and simple; that it does not need psychotherapy but rather psychosocial support or the instructions of a medical expert; and that it is better accepted by patients, probably due to their greater participation in decision-making.
9. Treatment with nalmefene, aimed at reducing alcohol consumption, better adapts to the needs of the majority of patients who start alcoholism treatment and can favor the acceptance of, adherence to and retention in the treatment program, and the commitment to this new therapeutic objective.
10. Nalmefene is the only drug which has been approved by the health authorities for use in reducing alcohol consumption in patients with alcohol dependence.

Conflict of Interests

The author participated as principal researcher in the ESENSE 2 study and has been a member of the Lundbeck España advisory committee on nalmefene.

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