SMGroup

Opioid Receptor Antagonists and Alcohol Dependence Treatment

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PART I: MECHANISMS OF ACTIONS

One of the features of human and animal behavior is the disposition for behaviours experienced as reinforcing to be more likely to occur in the future. In the case of alcohol consumption, the reinforcing effect can happen for two reasons: a) positive reinforcement: alcohol induces satisfying conditions that stimulate new consumptions; with repeated use of alcohol, drinking and stimuli associated with it gradually become more attractive, leading to a loss of control and creation of an impulse focused on alcohol consumption; b) negative reinforcement: alcohol is consumed to relieve or avoid withdrawal symptoms; the reduction or suspension of the substance gives rise to neurodegenerative and affective disorders, with alcohol consumption arising from the need to suppress such negative changes [1].

Both positive and negative reinforces are condition the desire to repeat the consumption of alcohol through processes mediated by neuronal changes. It's when, how and where such changes occur, that transform the individual into an alcohol dependent person, is the goal of the neurobiological studies on alcohol, aiming that such knowledge may contribute to reduce the consequences of alcohol abuse and foster better therapeutic interventions (Figure 1).

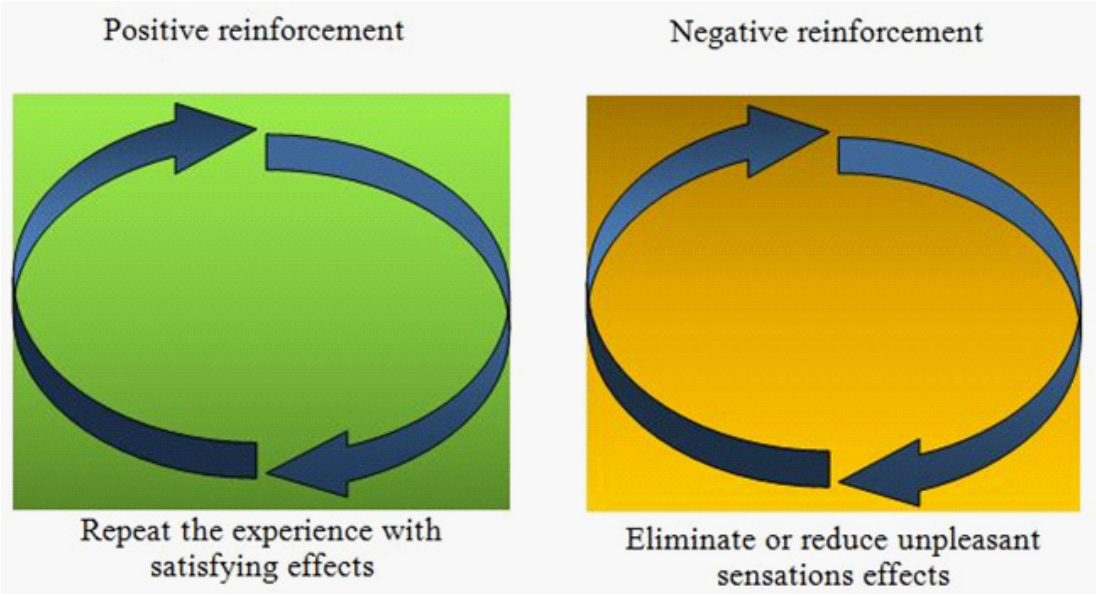

Figure 1: Positive and Negative Reinforcement.

DOPAMINE AND THE BRAIN REWARD SYSTEM

When explaining the satisfying action of alcohol, there is abundant evidence that ethanol promotes activation of the mesolimbic-mesocortical dopaminergic path. These bundles project from the ventral tegmental area **(VTA)** to the dopamine receptors **(DA)** located in the *nucleus accumbens* **(NAc)** and other mesolimbic areas, such as the hypothalamus, amygdala, hippocampus, septal area and pre-frontal cortex [2-5], constituting the central circuit of the brain reward system involved in the regulation of mnemonic processes learning of motivated behaviours, modulation of affection and externalization of emotions by activating motor pathways. Repeated stimulation of dopaminergic neurons by the action of alcohol, associated with the release of DA in the *nucleus accumbens*, emerges as the key mechanism for the onset and maintenance of alcohol consumption preference [2,6].

Numerous animal studies show the increase in extracellular levels of dopamine in the *nucleus accumbens* [2,7,8] and amygdala [9] after injection or self-administration of alcohol, with such increase being higher in alcohol-preferring genetically selected animals, which indicates the influence of genetic factors in the activation of dopamine and, ultimately, in the reinforcing properties of alcohol [7,10].

Genetic polymorphism has also been evidenced in clinical and laboratorial studies in humans, highlighting the participation of allele variants of the D2 and D4 receptor genes in vulnerability to alcohol dependence [11-14]. On the other hand, studies carried out in young people at high risk of alcohol dependence show greater increase in extracellular DA levels than the control groups without this associated risk [15].

Besides the release of DA, alcohol also affects DA receptors, particularly the D2 receptor. Studies using different methodologies found that strains of alcohol-preferring genetically selected animals are distinguished by the reduction of D2 receptors concentration in the limbic system [16], whereas human subjects with alcohol dependence show a lower affinity with D2/D3 receptors than the control groups [17-20], suggesting an increased vulnerability to substance abuse. Observations carried out both in animals and in humans associate high levels of D2 receptors to more intense responses to alcohol intoxication, which seems to constitute a protective factor against substance abuse, whereas subjects with low levels of D2 receptors show a more attenuated response and greater propensity for continued consumption of alcohol and increased risk of alcohol dependence [16-18,20-22]. D1 receptors also seem to be involved in a down regulation system in response to alcohol but results have been less conclusive [23].

DA receptors agonist and antagonist substances have led researches to inconsistent results, showing that both have a reducing action of the reinforcement induced by alcohol, favouring the reduction of consumption. Agonist substances (bromocriptine, lisuride, apomorphine, modafinil) reduce dopamine deficit and reverse the preference for alcohol, but the success observed with animals was not seen in humans [24-27]. In the second case, antagonist agents (haloperidol, tiapride, risperidone, flupentixol) reduce the hyperactivity induced by low doses of alcohol, attenuate the reinforcing effect of drinking and decrease symptoms associated with withdrawal syndrome, an action related to the affinity for D2 receptors [28,29] but evidence of efficacy in maintaining abstinence are scarce [27-30].

In convergence with the positive reinforcement hypothesis, the dopaminergic system is also involved in the negative reinforcement effect of alcohol. Animals with symptoms of alcohol withdrawal present levels of extracellular dopamine below normal in the *nucleus accumbens*; as the reduction of dopamine in this area of the brain may predict depression/dysphoria, this change plays an influential role in the symptomology of alcohol abstinence and negative reinforcement that accompanies this syndrome [31,32]. It was found recently that chronic exposure to alcohol changes the function of D2 and D4 receptors in the pre-frontal cortex, with these changes being maintained during the initial stages of abstinence, which contributes to the deficit of executive functions, such as decision making and cognitive control of behaviour, even after cessation of ethanol consumption [33]. Linking these actions there is a two-phase model that differentiates low consumption situations from abuse/dependence situations [32]. In low consumption situations, alcohol triggers a complex set of stimuli and responses that lead to a feeling of well-being and

ultimately to positive reinforcement. In cases of continued, excessive consumption, disruption of cellular interactions leads to a two-stage process: in the first stage, alcohol causes a brief feeling of well-being associated with the release of the neurotransmitters in the reward circuits, but as ingestion of alcohol continues, the synthesis and release of neurotransmitters changes, causing deficit of brain messengers, along with anxiety, irritation, or craving, and leading to a repeated self-sustained search pattern for alcohol [32].

Several mechanisms have been proposed to explain the influence of ethanol over dopaminergic activity but the process remains under discussion [4,6,34-36]. Regardless of the mechanism involved, some researchers consider the "dopaminergic hypothesis" as the neurochemical explanation that best explains the development of motivation and dependence from alcohol [1,3] whereas others consider that the simple activation of the dopaminergic system is insufficient for understanding the mechanisms underlying the feeling of pleasure and reinforcement induced by alcohol and even claim not to be necessary the integrity of mesolimbic dopaminergic neurons to cause the alcohol dependence process [35]. Currently, data point to the existence of neuro circuits through which the endogenous opioid system acts in the release of DA in the *nucleus accumbens* and the mechanisms responsible for the ethanol reinforcing effects [34,37-40].

ENDOGENOUS OPIOID SYSTEM

Endogenous opioid peptides are non-classical neurotransmitters with an activity similar to that of opioid analgesics. Based on the pharmacological profile, three different subfamilies were initially identified and characterized – endorphins, enkephalins and dynorphins – and three types of inhibitory G protein-coupled receptors, designated as *mu* (μ), *kappa* (κ) and *delta* (δ) (respectively MOP, KOP and DOP, using the terminology recommended by IUPHAR - International Union of Pharmacology) [41]. Later on, new families were isolated, named nociceptin and endomorphins, but their functions and clinical relevance are still under study [42-44].

Endogenous opioid peptides originate from inactive precursor molecules (pro-opiomelanocortin - **POMC**; pro-enkephalin; pro-dynorphin), with similarities in the organization of their genes, which suggests a common ancestor [42]. The processes by which precursor molecules form active peptides are not equal in all tissues and the same precursor may lead to different products depending on the tissue and the receive signal. Through a set of tissue-specific enzymatic stages, the precursor protein pro-opiomelanocortin originates the melanocyte-stimulating hormones **(MSHs)**, corticotrophin **(ACTH)** β-lipotropic pituitary hormone **(β-LPH)** and four types of endorphins (α, β, γ, δ) including β-endorphin, the most powerful endogenous opioid peptide neurotransmitters [45]. Pro-enkephalin originates two forms of enkephalin, the methionine-enkephalin (met-enkephalin) and the leucine-enkephalin (leu-enkephalin). Pro-dynorphin encodes dynorphins, chains of amminoacids with different lengths, with the leu-enkephalin sequence: dynorphinA, dynorphin B and α/β-neo-endorphin [36,42,45].

The opioid compounds and their receptors form the endogenous opioid system, involved in a large group of functions encompassing the control of feelings, emotions and affection: modulation of response to painful and stressing stimuli; reward and reinforcement; homeostatic adaptive functions, such as body temperature regulation, ingestion of food and water, reproduction [36,42].

Both the endogenous opioid peptides and the opioid receptors are widely distributed by the central nervous system **(CNS)** and peripheral nervous system **(PNS)** mediating the neuromodulator or neurotransmitter functions [37-39]. The β-endorphin is produced by the anterior pituitary, being released into the peripheral systemic circulation, and by the hypothalamic POMC neurons and released in the CNS. The β-endorphin produced in neurons is present in the ventromedial arcuate hypothalamic nucleus and projected to other areas of the hypothalamus (supraoptic nucleus, paraventricular nucleus, and lateral hypothalamus) as well as to the amygdala, ventral tegmental area **(VTA)**, periaqueductal gray and bed nucleus of the *stria terminalis* [46,47]. It is released during pain and stress situations, causing an analgesic effect and reducing the anxiety and causing feelings of euphoria [45].

Enkephalins are also released by neurons in the central nervous system and by cells in the adrenal medulla; in the CNS, they can be found in most brain regions including most hypothalamic and thalamic nucleus, preoptic area, septum, *nucleus accumbens*, ventral tegmental area, amygdala and neocortex, participating in a large number of effects including perception of pain, regulation of memory and emotional conditions, ingestion of food and liquids, immune responses and control of the gonadal function [46]. Dynorphins have been identified in many different parts of the brain (hippocampus, amygdala, hypothalamus, striatum, spinal cord) and intestine and play a regulatory role in numerous functions involving analgesia, reinforcement, stress response, cognitive function (learning and memory) and motor integration [45,48].

Once synthesised and stored in neuronal vesicles, opioid peptides are released in response to specific stimuli that cause depolarization of the neuronal membrane. Opioid peptides disseminate into the synaptic area to interact with the various classes of opioid receptors present on both pre and post-synaptic membranes of opioid and opioid target neurons, located close to the release area (enkephalines) or more distant areas (β-endorphines, dynorphines) [39], being rapidly deactivated at extracellular level by the peptidase enzymes which breakdown active peptides to produce inactive metabolites. Blocking the inactivation of opioid peptides increases their basal extracellular levels near the release site [43,49].

The relationship between endogenous opioid peptides and their receptors is complex. β-endorphins bind with about equal affinity to μ and δ-opioid receptors, whereas enkephalins bind with much greater affinity to δ-opioid receptors than to μ-opioid receptors, and dynorphins tend to bind selectively to κ-opioid receptors [36,37,42,50]. Opioid receptors have various sub-types (μ1, μ2; δ1, δ2; κ1a, κ1b, κ3, κ4) [51] so the results of such interactions must be carefully assessed, avoiding any generalization; however activation of μ- and δ-opioid receptors frequently

leads to euphoria patterns whereas stimulation of k-opioid receptors is associated with dysphoria [37,50,52]. For instance, in the mesolimbic system, β-endorphins and enkephalins mediate the increase of DA release in the *nucleus accumbens* through interaction with μ- and δ-opioid receptors, actively participating in the reward and reinforcement processes [37,38,53]. Dynorphins, on the other hand, lead to inhibition of DA release as a result of activation of k-opioid receptors, creating aversive states [53]. Although it seems that the various sub-types of opioid receptors have a relatively equivalent distribution in rodents brains and in the human brain, differences have been reported that must be considered when using animal models; these differences include a larger k receptor mRNA expression in different areas of the brain, k and μ receptors in the cortex and hippocampus and μ-opioid receptors in the hypothalamus of humans, compared to rats [37,52].

ETHANOL AND ENDOGENOUS OPIOID SYSTEM INTERACTIONS

Although there is a very considerable number of researches that show changes in endogenous opioid peptides as a result of alcohol ingestion, the mechanism of interaction of these molecules in alcohol dependence is still not sufficiently clarified [36-38,40,54,55].

Acute administration of ethanol stimulates the dose-dependent release of endorphins and enkephalins in the hypothalamus and pituitary gland of rodents [36,39,56]. But, although studies have been relatively conclusive on endorphins, the results of ethanol action on the release of enkephalins are contradictory [37,40,50]. Less information is available on dynorphins but studies point to an increased release in the *nucleus accumbens* with exposure to very high doses of alcohol, which may be associated to an aversive effect [48,50,57].

As to extended exposure to alcohol, there is generally a decrease in the positive reinforcement properties from the endogenous opioid system [37,51]. Chronic administration of alcohol decreases POMC gene expression, β-endorphins release and μ-opioid receptors affinity [58], while increasing pro-dynorphins and dynorphins involved in the negative reinforcement effect of alcohol [59-61].

Assessment of ethanol effect over opioid receptors proves to be more difficult, with results depending on the studied areas of the brain, the experimental conditions of alcohol administration and the species and strain of animals studied [36,37]; consequently, studies are frequently inconsistent [36].

An important source of data on the involvement of the endogenous opioid system in alcohol dependence derives from studies in animals and humans with a genetic predisposition for alcohol consumption.

Rats belonging to selected strains due to their high preference for self-administration of alcohol show lower levels of endogenous opioids before alcohol consumption and, compared to animals without such preference **(NP)**, the ingestion of ethanol causes an increased release of hypothalamic β-endorphins [36,56,62] and a higher genetic expression of the hypothalamic

[56,62-64] and pituitary gland [65] mRNA POMC. In what concerns enkephalin levels, there are also differences in P and NP strains, with the former showing higher levels of enkephalin in the *nucleus accumbens*, ventral tegmental area [60] and hypothalamus [66] and higher pro-enkephalin mRNA expression in the pre-frontal cortex [63]. In a study where met-enkephalin levels were similar in the striatum, hypothalamus, medulla and pons, the strain with higher pre-disposition for voluntary ethanol consumption had lower pro-enkephalin concentration and met-enkephalin in the mid brain and exhibited marked mesolimbic enkephalin increase following voluntary ethanol consumption [67]; In the same sense, in another study, both strains of animals showed equal baselines of pre-proenkephalin mRNA **(PPENK mRNA)**; after infusion of alcohol rats selected due to preference for alcohol showed a significant increase in PPENK mRNA in the *nucleus accumbens* [68]. With dynorphins, results are different, showing a higher number of binding areas and affinity for these peptides and for pro-dynorphin mRNA in the *nucleus accumbens* and septum of ethanol-avoiding mice [69].

Likewise, the alcohol-preferring strains vs alcohol-aversive strains have showed differences in the distribution of opioid receptors. The alcohol-preferring strains tend to show higher density of μ-opioid receptors in the *nucleus accumbens* area and other limbic system structures and in the pre-frontal cortex area [63,70], higher density of δ-opioid receptors in the ventral tegmental area and *nucleus* [71] and lower density of κ-opioid receptors in the ventromedial hypothalamus [63] and *nucleus accumbens* [69] than alcohol-aversive rats. In the past decades, studies performed with genetically manipulated animals showed that animals without the μ-opioid receptor (knockout μ) present a reduction in voluntary alcohol consumptions whereas animals without the δ-opioid receptor (knockout δ) present an increase [72].

Although not being conclusive as to a causal relation, these results suggest a relation between the opioid system and the self-administration of ethanol, highlighting the fact that, in general, these studies show that alcohol-preferring strains present low levels of β-endorphin and enkephalin activity in several areas of the brain, at baseline, and a significant increase as response to acute ethanol exposure [36,56,73].

Similar results were observed in humans. Non-alcohol dependent adults with alcohol dependent parents (high risk group) show lower baseline levels of β-endorphins than non-alcohol dependent adults without a history of alcohol dependence in the family (low risk group) [73]; with alcohol, adults with alcohol-dependent parents show a marked increase of β-endorphins when compared to adults with non-alcohol dependent parents, tending to equate the final results [73,74] although not all studies confirm this discrepancy [75]. Comparing alcohol dependent and non-dependent adults, the former show lower levels of β-endorphins both in plasma and in the CFS, regardless of the alcoholisation time [76,77] which strengthens the hypothesis of β-endorphins binding with a higher sensitivity to alcohol and to genetic pre-disposition to alcohol dependence. Recent studies using PET in humans showed that alcohol causes the release of endorphins in the *nucleus*

accumbens **(NAc)** and orbitofrontal cortex **(OFC)** both in individuals with high consumption of alcohol and in healthy control individuals, with a greater increase in the first group with a positive correlation between changes in the OFC and the extension of alcohol-related problems and the subjective sensation of intoxication [78].

The complexity of the relation between the endogenous opioid system activity and the development of alcohol dependence originated contradictory theories, such as the opioid deficit theory [79,80] and the opioid surfeit theory [81]. Other models relate the opioid system and the use of alcohol to stress and individual differences in the opioid system to alcohol sensitivity [46,74].

In stress-inducing situations, the hypothalamus-pituitary-adrenal **(HPA)** axis is activated mainly by the production of the corticotropin-releasing hormone **(CRH)** which is transported to the receptors on the anterior pituitary and originates the production of β-endorphins and ACTH from its precursor POMC. ACTH influences the adrenal gland to stimulate the release of glucocorticoids. Between the production of endogenous opioids and the production of ACTH there is a negative feedback effect, i.e., endogenous opioids may inhibit the production of ACTH [82]. Similarly to stress, alcohol also stimulates the synthesis of CRH in the hypothalamus and activation of the HPA axis [76,83] with subsequent synthesis and release of endogenous opioids thus contributing to the alcohol reinforcement properties.

Throughout researches, evidence has been stacking on the relation between alcohol consumption and changes in the HPA axis function and the activity of the endogenous opioid system, both in animals [55] and in humans [74,84,85]. Among other data these studies suggest that: reduced β-endorphines baselines and exaggerated responses to stress induce a higher vulnerability to ethanol abuse [86]; the chronic deficiency of β-endorphines is associated with states of higher anxiety and increase of sensitivity to ethanol rewarding properties, at least partially, as it relieves anxiety [55]; reduction of β-endorphins and ACTH activity with chronic consumption of alcohol [84] and deregulation of the HPA axis in withdrawal syndrome [87]; reduction of ACTH response or cortisol response to stress predicts an earlier return to drinking [87]; β-endorphin plasma levels are inversely related to anxiety self-assessment levels during withdrawal [88]. Non-dependent individuals with a family history of alcohol dependence show higher baseline levels of ACTH and an intense endocrine response to stress, dampened by alcohol administration [85]. In summary, these studies point to the fact that alcohol-induced reduction of increased baseline levels of anxiety are a strong factor for negative reinforcement regarding alcohol dependence maintenance [55,85,88,89].

A relevant set of studies supporting alcohol interaction with the endogenous opioid system derives from the use of pharmacological agents acting over the system receptors.

These studies show that μ- and δ-opioid receptors agonists (e.g.: morphine, DAMGO, DALA, DPDPE) increase the release of DA [38,53] and alcohol consumption in laboratory animals

[90], whereas opioid receptor antagonists (naloxone, naltrexone, nalmefene) compete with the endogenous opioid peptides for binding to the opioid peptide receptor and reduce the alcohol-induced dopaminergic activity [38,91], reduce consumption, both in animal models [90,92] and in humans [93-95], reduce craving [96] and relapses [94,97].

Overall, researchers suggest a strong participation of the endogenous opioid system in the stimulation and reinforcement of alcohol consumption. As such, there is a consensus that comprehension of basic mechanisms favouring onset and maintenance of alcoholic drinks consumption must include the intervention of neuropeptides and opioid receptors. Many of the mechanisms underlying the interaction between the opioid system and other neurotransmitter and neuromodulator systems (serotonergic, GABAergic, noradrenergic, colinergic, cannabinoid…) [39,40,47] are still unclear, as well as the meaning and significance of such changes in alcohol addictive behavior. Not with standing, researches and empirical studies have already led to a point where two out of the four substances approved for pharmacological treatment of alcohol dependence are directly related to the endogenous opioid system.

PART II: CLINICAL PERSPECTIVE

FROM N-ALLYLNORCODEINE TO NALTREXONE AND NALMEFENE

The History of Opioids receptors antagonists began in 1915 when von Julius Pohl first describes the ability of N-allylnorcodeine to reverse effects of morphine and heroin on respiratory depression [98]. But it was not until the 1950s, that Pohl's works are updated and utilized by Hart to synthetized N- allylnormorphine (Nalorphine), an antidote for morphine with analgesic properties [99-102]. However, because of its dysphoric properties, it was rapidly abandoned. Then surged pentazocine and cyclazocine. Cyclazocine have been extensively studied for it potential in opiate addiction, despite promising results, the induction of sleepiness, drunkenness and in some cases hallucinations and respiratory depression prevented its used in clinical practice [103-108]. Naloxone, an allyl derivative of noroxymorphone and the first opioid antagonist reaching important clinical application, became the treatment of choice of opioid overdose [109]. If on one hand, naloxone was a pure opioid antagonist[1] with fewer adverse effects than its predecessors, on the over hand its poor oral bioavailability and short duration of action limited its use for the treatment of opioids or alcohol dependence [110-112]. In an attempt to avoid these disadvantages, Endo laboratories synthesized in 1963, Endo 1639A, a cyclopropylmethyl analog of naloxone, rename Naltrexone [113,114]. It's a relative pure and potent μ-opioid antagonist with longer duration of action and better bioavailability then naloxone [115]. Rapidly it becomes a treatment of choice for opioid addiction and in 1994 was approved by the American Food and drug Administration for the treatment of alcohol dependence. Finally, in 2012, Nalmefene, an opioid antagonist, structurally and functionally related to Naltrexone was approved by the European Medicines Agency **(EMA)** for the treatment of alcohol dependence (Figure 2).

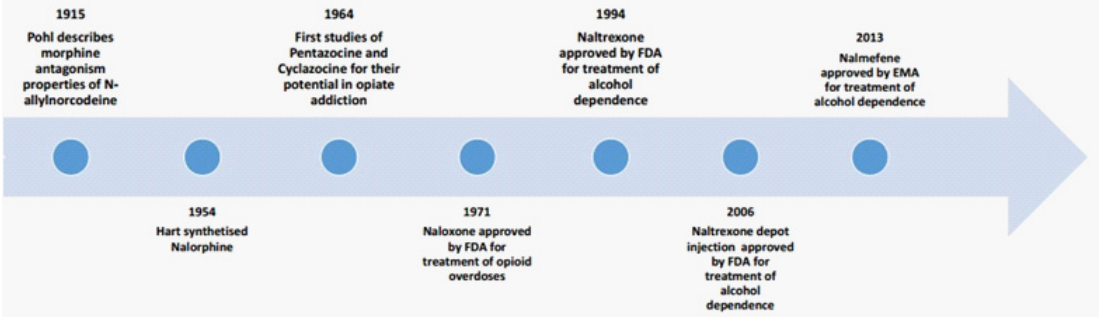

Figure 2: From N-allylnorcodeine to Naltrexone and Nalmefene.

NALOXONE THE PRECURSOR

Naloxone is an allyl derivative of noroxymorphone and a potent non-selective opioid antagonist, with an affinity order of: μ > κ >> δ- opioid receptors [110,116] (Figure.3). It was the first opioid antagonists evidencing potential efficacy as a treatment for alcohol dependence in animal experimentation. For example, Naloxone abolishes the preference for alcohol developed by rats after 15 days of administration of an ethanol solution [117]. The injection of Naloxone also decreased alcohol self-administration, in rats educated to press a lever to obtain water or alcohol, [118]. This suppressing effect on alcohol intake, was also observe in rats which were selectively bred alcohol preference [119]. However, despite this potentialities, its short duration of action, reduce bioavailability, the need of very high doses to sustain opiate blockade (2 - 3g for 24h), and the discovery of new opioid antagonists, like naltrexone, prevented its clinical use for the treatment of alcoholism in man [112,120,121].

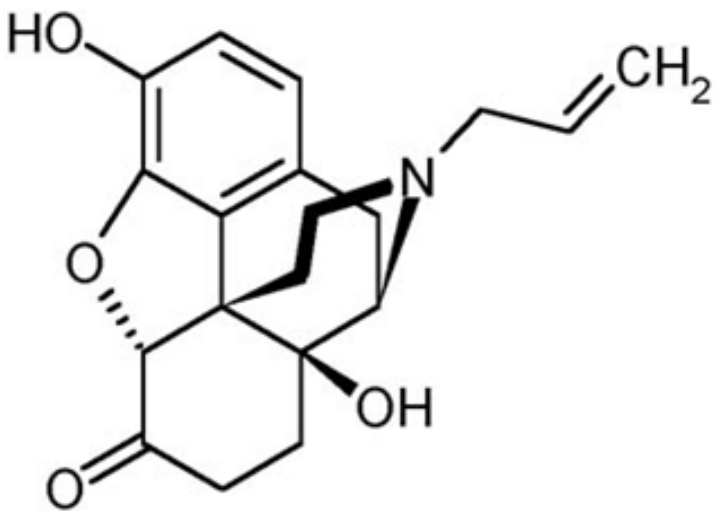

Figure 3: Chemical structure of Naloxone.

NALTREXONE FOR THE TREATMENT OF ALCOHOL DEPENDENCE

Chemistry and Mechanism of Action

Naltrexone is ancyclopropyl derivative of oxymorphone, structurally similar to naloxone and is also an opioid antagonist with a high affinity for μ-opioid receptors, an intermediate affinity for κ-opioid receptors, and a very low affinity for δ-opioid receptors [116,122,123] (Figure.4). It is believed that naltrexone blocks opioidergic inhibition of GABAergic inhibitory interneurons in the ventral tegmentum area and by so blocks release of dopamine in the nucleus accumbens, neutralizing the increase in dopaminergic neurotransmission produced by alcohol consummation, and ultimately diminishing its pleasurable effects [124]. Orally, is well and rapidly absorbed, but suffered an extensive first-pass metabolism in the liver, where it is metabolized to 6-β-naltrexol. It is mainly excreted in the urine. The Half-life of Naltrexone range between 4 and 10 hours dependent on the duration of the administration, and is of 12 to 16 hours for 6-β-naltrexol [125,126].

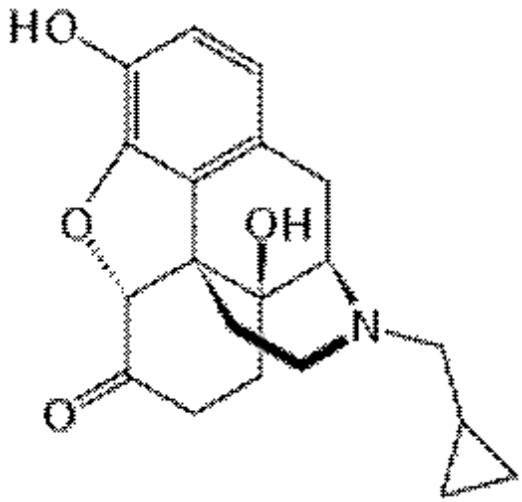

Figure 4: Chemical Structure of Naltrexone.

Efficacy

Naltrexone efficacy in the treatment of alcohol dependence was initially supported by two double blind, placebo-controlled trials of Volpicelli et al and O´Malley et al. They evidenced that 50mg of oral Naltrexone in adjunct with psychosocial alcohol rehabilitation programs (Volpicelli study) or Coping Skills Therapy oriented for abstinence (O´Malley study), significantly decreased alcohol craving, mean of drinking days, and rates of relapse [93,94]. A large multicenter study, the COMBINE study, demonstrated that 100mg of oral Naltrexone associated with medical management is more effective than placebo or Acamprosate in reducing drinking days and heavy drinking [127, 128]. Compared to placebo, Naltrexone reduced percent days of abstinence

in 5,5% (p=0,02) and risk of heavy drinking days (hazard ratio, 0.72; P=.02) [127]. Many over studies with different endpoints and different adjunctive treatments confirm the effectiveness of Naltrexone in alcohol dependence. However, an important multicenter clinical trial sponsored by the Department of Veterans Affairs which enrolled men with chronic and severe alcohol dependence found no significant differences between Naltrexone and placebo for the prevention of relapse, or for reducing the amount of drinks per day. Finally, a recent Cochrane review based on 50 trials including 7793 patient, concluded that Naltrexone is a safe and effective strategy in alcoholism treatment with a moderate size effect in the reduction of heavy drinking and drinking days [129]. On this review Naltrexone was found to reduced drinking days by 3,9%, and the risk of heavy drinking by 83% [129].

Management

Naltrexone Hydrochloride (REVIA®; DEPADE®), was approved by the US Drug and Food Administration (FDA) in 1994 for the treatment of alcohol dependence as part of an appropriate plan management for the addiction. The treatment should be initiated after at least 3 days of abstinence, and a medical evaluation with physical exam, psychosocial evaluation and laboratory testing including liver enzyme and screening test for drugs of abuse must precede the prescription. Naltrexone should be start at 25mg per day and increase to a maintenance dose of 50mg per day for up to 6 month or longer if the patient wants to continues. However, the drug should be stopped if drinking persist 4 to 6 week after initiating Naltrexone [130-132].

The 2011 NICE guidelines distinguish two situations in which Naltrexone can be used [131]:

- First, after a successful withdrawal, Naltrexone can be considered in combination with a psychological intervention, in moderate and severe alcohol dependence. The aim is to maintain abstinence.
- Secondly, Naltrexone in combination with a psychological intervention can be used for harmful drinkers and people with mild alcohol dependence who has not responded to psychological interventions alone.

The 2009 Treatment Improvement Protocol of the U.S. Center for Substance Abuse Treatment Highlights that oral Naltrexone should be used in patients who are highly motivated or associated to a medication monitoring plan. It is also put forward that Naltrexone in patient with intense craving or with a family history of alcohol dependence may be more beneficial [130,132].

The 2015 French guidelines of the *Société Françaised' Alcoologiesubline* that Naltrexone associated with psychosocial intervention is a first line treatment for preventing relapses after alcohol withdrawal [133].

Adverse Effects and Limitations of Use

Some mild and time limited side effect can be experience in up to 30% of patient, including gastrointestinal symptoms, like nausea, vomiting, or abdominal pain, and symptoms associated

with a decreased arousal, like fatigue, sleepiness or weakness. Decreased libido and depression can also be experienced [129]. Naltrexone in High doses (100 to 300mg/day) was associated with hepatotoxicity in studies with obese patient and that why liver enzymes should be monitored and Naltrexone is contraindicated in liver failure [134,135]. Another concern is about patient using illicit opioid drugs, buprenorphine, methadone, opioid analgesic or medications containing an opioid, because of the necessary risk of acute withdrawal syndrome, and is contraindicated in this cases [130,132].

Extended-Released Injectable Naltrexone (XR-NTX)

Although evidencing efficacy, oral Naltrexone have several limitations, and adherence is probably the big one. Specific studies point out the impact of adherence on efficacy, for example a multicenter, randomized, double blind clinical trial comparing Naltrexone and placebo in 175 patient find no differences in drinking outcomes, however when only compliant patient where analyzed, Naltrexone appears to be superior to placebo [136]. Another one comparing Naltrexone and placebo in 97 patients also evidenced comparable results [137]. A reanalyzes of two major clinical trials that failed to encounter efficacy of Naltrexone over the placebo also revealed that medication compliance enhanced the effect of naltrexone [138]. Alongside with these clinical trials, naturalistic data are even more striking. A retrospective analysis of two commercial, community-based, claims database revealed that of 1138 patients who were prescribed oral Naltrexone and filled an initial prescription, 51,8% filled only one prescription and the vast majority (85,8%) didn't persist on Naltrexone (defined as having filled prescriptions for ≥80% of the 6-month treatment period) [139]. They also evidenced that non-persistent patient had a poorer outcome with significantly more emergency room admission and hospitalizations. In the same way another retrospective analysis of a claims database evidenced an even poorer treatment adherence [140] (Figure 5).

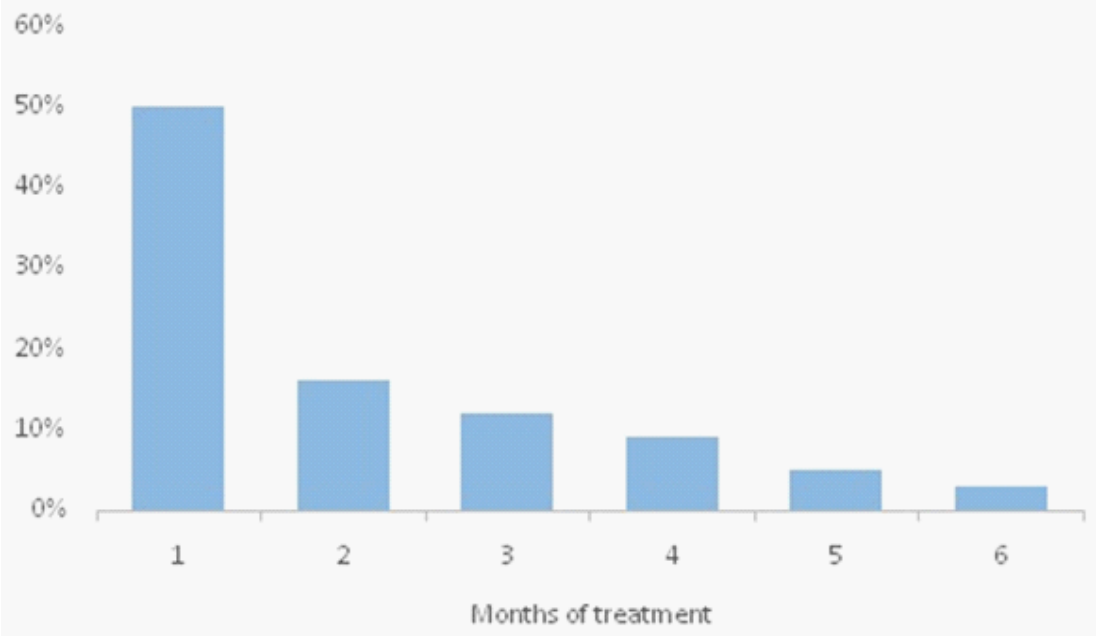

Figure 5: Estimated adherence to oral Naltrexone across time based on literature data.

It is in this context that a Naltrexone sustained-release formulation is meaningful.

In fact, an extended-released injectable suspension of Naltrexone (VIVITROL®) was approved by the U.S. FDA for the treatment of alcohol dependence in 2006. It is a formulation containing microspheres of polylactide-co-glycolide loaded with Naltrexone. An injection contains 380mg of Naltrexone and has to be administered into the gluteal muscle once every 4 weeks. XR-NTX avoid first-pass hepatic metabolism permitting a monthly total doses 4-fold less in comparison with oral Naltrexone. Moreover XR-NTX yield plasma area under the curve 3 to 4 times higher than oral Naltrexone, with more stable levels [141].

The efficacy of XR-NTX was demonstrated in a multicenter randomized controlled trial including 624 participants, receiving a monthly injection with XR-NTX 380mg, XR-NTX 190mg or placebo, combined with a 12 sessions of low-intensity psychosocial intervention. Compared with placebo XR-NTX 380mg decreased in 25% the rate of heavy drinking days [142]. A secondary analysis of outcomes determine that XR-NTX 380mg was more effective in reducing drinking days and heavy drinking days in patient with at least 4 days of abstinence, while XR-NTX show intermediate results indicating a dose-effect response [143]. A Cochrane review indicate that XR-NTX reduced the risk of any drinking after detoxification to 92% of the placebo [129].

XR-NTX have a safety profile similar to oral Naltrexone excepted for injection site reactions, and theoretically lower risk of liver toxicity because of its lack of first-pass hepatic metabolism, and reduced doses [129,142].

The 2009 Treatment Improvement Protocol of the U.S. Center for Substance Abuse Treatment suggest that XR-NTX is probably a better option for patient in which adherence to oral medication is an issue or in those who prefer not have to remember to take daily oral medication [132].

Factors Influencing the Response to Naltrexone

Numerous potentials factors associated with a better response to Naltrexone in alcohol dependence have been suggested like: family history of alcoholism [144-147]; history of abuse of other substances [144]; onset of alcohol abuse before age 25 [144,148]; higher levels of craving [145,149]; antisocial traits [146]; high baseline depressive symptomatology [148]; type III and IV of Lesch's typology [148]; poor cognitive functioning [149]; Asn40Asp polymorphism of the μ-opioid receptor [150,151]; male gender [142,152]; type A of Babor's typology [153].

Of this, only Family History of Alcoholism and Asn40Asp polymorphism of the μ-opioid receptor has a consistent evidence of improving the effect of Naltrexone in patient with alcohol dependence [154]. However, the overall strength of evidence is weak, based on few studies with a high risk of bias.

NALMEFENE FOR THE TREATMENT OF ALCOHOL DEPENDENCE

Chemistry and Mechanism of Action

Nalmefene is a 6-methylene derivative of naltrexone, with high affinity at μ and κ-opioid receptors, and moderate affinity at δ-opioid receptor (Figure.6). It functions as an antagonist at μ and δ-opioid receptors and as partial agonist at κ-opioid receptors [155-158]. In one experimental study Nalmefene was found more effective than Naltrexone to suppressed alcohol self-administration in alcohol-dependent rats, but similar to Naltrexone in nondependent rats [159]. The differential binding profile of Nalmefene, and especially it's high affinity and partial agonist properties on κ -opioid receptors is advanced to explain this differential effect on ethanol dependent rats. Other beneficious differences relative to Naltrexone are: a better bioavailability [160], a longer plasma half-life [161], a longer occupancy of central μ-opioid receptors [161], resulting in a longer duration of action and no association with hepatotoxicity even with high doses [162].

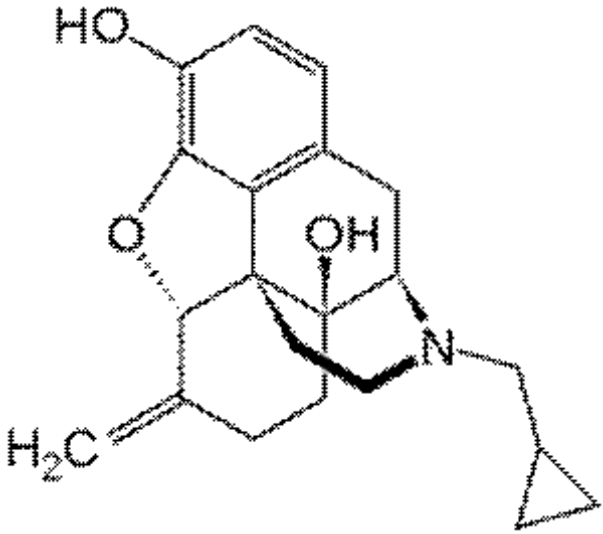

Figure 6: Chemical structure of Nalmefene.

Efficacy

Several studies evidenced the efficacy of Nalmefene for the treatment of alcoholism, but in a different fashion then Naltrexone, indeed in most studies the main goal was not abstinence but reduction of alcohol consumption with an as-needed administration of Nalmefene in patient who are not previously abstinent [163-166].

Three large multinational, randomized, double-blind, placebo-controlled, European trials support the efficacy of Nalmefene and leads to it approval by the European Medicines Agency (EMA). ESSENSE 1 and ESSENSE 2 trials evaluated the efficacy of as-needed Nalmefene distributed to adult with alcohol dependence in reducing alcohol consumption in a 6-month period. ESSENSE 1 found that Nalmefene reduce the number of heavy drinking days (-2,3 day; p=0,0021) and total alcohol consumption (-11,0g/day; p=0,0003)(164). ESSENSE 2 shows similar but less significant results, with a reduction of heavy drinking days (-1,7 day; p=0,0,12) and of total alcohol consumption (-5,0g/day; p=0,088) [165]. A post-hoc analysis of this two trials conclude that Nalmefene is more effective for patient with a high drinking risk level (men: >60 g/day; women: >40 g/day) [167].

SENSE trial evaluated the efficacy and safety of as-needed Nalmefene in a one year period, concluding that Nalmefene is more effective than placebo in reducing the number of heavy drinking days (-1,6 day /month; p=0,017) and the total alcohol consumption (-6,5g/day; p=0,036) [166]. SENSE trial also concluded for the long-term safety of as-needed Nalmefene, evidencing mainly mild and transient adverse events. These 3 trials included a total of 1997 patients, and all included a motivational and adherence-enhancing intervention named BRENDA.

Management

Nalmefene (SELINCRO®) was approved by the EMA in 2013, for the reduction of alcohol consumption in alcohol dependent patients [168]. Contrary to Naltrexone, Nalmefene is to be taken on an as-needed basis. 1-2 hours preceding the perceived moment of drinking, the patient had to take one tablet of Nalmefene 18 mg, or as soon as possible if the patient had already start drinking. The drug is indicated for patients with alcohol dependence who have a high drinking risk level, without physical withdrawal symptoms and who do not require immediate detoxification. The marketing authorization also subline that Nalmefene should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption. Finally, the drug should be initiated only in patients who continue to have a high drinking risk level two weeks after initial assessment. Nalmefene has already been integrated in French and NICE guidelines (133, 169), but is not already approved by the FDA for this indication.

Adverse Effects and Limitations of Use

Adverse effects are globally similar to that of Naltrexone including nausea, insomnia, dizziness, headache, fatigue and decreased appetite [166]. They are usually of mild and moderate intensity, and have a short time duration (1 to 7 days), associated with the treatment initiation. Contrary to Naltrexone high doses were not found to be associated with hepatotoxicity. A report of overdose with 450mg of Nalmefene didn't evidence alteration of vital functions [168]. As with Naltrexone, special cautions are to be taken with opioid addicts and patient taking medications containing an opioid.

Table 1: Comparison of Naltrexone and Nalmefene in alcohol dependence treatment.

	Naltrexone	Nalmefene
• **Formula**	$C_{20}H_{23}NO_4$	$C_{21}H_{25}NO_3$
• **Trade name**	REVIA®; DEPADE®; VIVITROL®	SELINCRO®
• **Route of administration**	Oral / Intra-muscular	Oral
• **Oral bioavailability**	~ 25%	~ 40%
• **Half-life**	~ 4h	~ 10h
• **How to use in alcohol dependence**	Initiate after detoxification, Orally: 50mg per day IM: 380mg every 4 weeks 6 month or more	Taken on an as-needed basis, 1-2h before the moment of drinking 18mg orally
• **Aim**	Maintaining abstinence	Reduction of alcohol consumption
• **Adverse effects**	nausea, vomiting, abdominal pain, fatigue, sleepiness risk of hepatotoxicity in high doses	nausea, insomnia, dizziness, headache, fatigue, decreased appetite
• **Main vantages**	Improved adhesion with depot formulation	Not associated with hepatotoxicity

Footnote

Although initially considered opioids antagonist, following studies demonstrated that Nalorphine and Cyclazocine are mixed opioid agonist/antagonist.

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