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The use of naltrexone in the treatment of alcohol dependence: pharmacological aspects

Przemysław Bieńkowski

Department of Pharmacology, Institute of Psychiatry and Neurology, Warsaw, Poland
Head of the Department: prof. dr hab. n. med. Przemysław Bieńkowski

Summary

Clinical studies performed over the past decades have unambiguously indicated that combined therapy, involving pharmaco- and psychotherapy, is an optimal approach to alcohol dependence. Both pharmaco- and psychotherapy should be personalised with a careful balance between the patient's needs and his/her clinical characteristics. The aim of the present article is to review the basic pharmacological features of naltrexone and its use in the treatment of alcohol dependence.

Key words: opioid peptides, naltrexone, opioid receptor antagonists, alcohol dependence

Introduction

According to some conservative estimates, harmful drinking and alcohol dependence affect at least 15 million people in the European Union. In Poland, alcohol dependence affects more than 800 thousand people [2, 12, 30]. At the same time, the effectiveness of even the most intense psychotherapy in the treatment of alcohol addiction is rather limited, and the popular in Poland and the United States "high threshold" programs aimed at the maintenance of complete abstinence, represent a therapeutic offer for a significant minority of patients [12,14,24]. Effective methods of treatment of alcohol dependence are therefore a typical, unmet medical need. One of the attempts to respond to this need is to promote the combined therapy, utilising the effectiveness of a variety of psychotherapeutic and pharmacotherapeutic approaches [1, 15]. The combined therapy, taking into account the achievements of modern psychopharmacology, is a method referred to in most expert recommendations and major reference works [1, 7, 15, 21, 26]. It appears that individualisation (personalisation) of the psychotherapeutic and pharmacotherapeutic approach is an underestimated issue in the long-term treatment of alcohol addiction [4, 14, 15, 26].

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Although the opioid receptor antagonist, naltrexone [16, 20], is not a new drug (i.e. one that was recently discovered and introduced into the medical practice), its position in the Polish health care system is far from settled. The drug is known to therapists providing treatment for opioid dependence, nevertheless its use in the context of alcohol dependence is not well established. Given the above, the aim of the article is to provide psychiatrists with some basic information on the pharmacological characteristics of naltrexone and its practical implications.

The article does not address many of the terms and concepts used in the diagnosis and treatment of addiction. Neither does it discuss in detail the pharmacology of alcohol or other available methods of alcohol dependence treatment. These issues have been discussed in a number of papers available to interested readers [2, 7, 8, 12, 22, 26].

Opioid peptides and opioid receptors in the central nervous system (CNS)

The endogenous opioid system is evolutionarily an old transmission system present in the central nervous system (CNS) of many mammals [25]. Opioid transmission is based on the production and release of opioid peptides (β-endorphin, enkephalins, dynorphin) and the effect of these peptides on specialised neuronal membrane receptors in many regions of the CNS, including brainstem structures and limbic areas [25, 28]. It is widely recognised that there are at least three – varied in terms of structure and function –- opioid receptor subtypes: mi (μ), delta (δ) and kappa (κ). Importantly, individual opioid peptides are characterised by varied affinity to the abovementioned subtypes of receptors, which is reflected in the diversity of the role of e.g. β-endorphin and dynorphin in the regulation of motivational and emotional states and behaviour (Fig. 1) [21, 27, 28].

Endogenous opioids and the reward system

In addition to the well-known role in pain modulation, the opioid system is an important part of the so-called brain reward system. Therefore, medications that affects the opioid system may also affect a number of behaviours aimed at the acquisition and consumption of natural (water, food, sexual partners) and chemical (alcohol, opiates, nicotine) rewards [10, 11, 18, 25]. It is worth stressing that mi (μ) opioid receptors are mainly responsible for initiating motivational processes and positive emotional states, and the stimulation of kappa (κ) receptors rather leads to inhibition, apathy, dysphoria, and even psychotic states (Fig. 1) [5, 28]. Contrary to popular beliefs, the opioid system generates not only positive motivational and emotional states. Activation and euphoria typical to stimulation of the mi receptors may be extremely different states from the state of anergy and dysphoria occurring after the activation of kappa receptors [5, 8, 27]. As it is the case with a number of transmission systems, even within the opioid system, there is an apparent "homeostatic" mechanism limiting excessive stimulation in one direction [11, 27, 28].

In the context of practical applications of opioid receptor blocking drugs, it is worthwhile mentioning that chronic administration of receptor antagonists (naltrexo-

ne, naloxone) may lead to adaptive responses in terms of the number and function of opioid receptors (*chronic* receptor blockade => *increase* in the number and function of receptors, i.e. up-regulation) [11, 27]. For the non-selective opioid receptor antagonists such as naltrexone, up-regulation appears to affect both, mi as well as kappa receptors [27]. Hence its net effects on the motivational and emotional processes, although always worth considering, may be relatively small.

Fig. 1 *page 120* shows a simplified diagram of opioid transmission and the physiological consequences of mi and kappa receptors activation. It also summarizes possible impacts of naltrexone on the opioid transmission within the reward system [11, 20, 28].

Alcohol and the opioid system

Endogenous opioids are directly or indirectly involved in the effects of many addictive substances, including nicotine, heroin, benzodiazepines and cannabinoids [25]. The relationship between the activity of the endogenous opioid system and alcohol consumption is one of the better documented discoveries of the modern psychopharmacology. Low plasma opioid activity may be a correlate of a family history of alcohol addiction, and one of the key central effects of *single* doses of alcohol, is activation of the opioid system [13, 25, 26]. It has been shown that alcohol increases the release of β-endorphin in the midbrain nerve cells.

Hence, alcohol drinking, according to some authors, may be a conscious or unconscious attempt to compensate for the deficit of opioid activity or to compensate for a defect of other transmission systems that generate positive emotional states [4, 6, 11, 20].

It is worthwhile mentioning that β-endorphin, through the activation of mi opioid receptors, disinhibits ascending dopamine mesolimbic reward pathways. Dopamine released from the mesolimbic pathways in the ventral striatum may induce motivational processes and enhance behaviours aimed at obtaining alcohol. It is assumed that, in the long run, this leads to the fixation of the harmful pattern of alcohol use [23, 26].

Notably, endogenous opioids may be responsible for positive reinforcing effects of alcohol in a mechanism independent from the above-described interactions with dopamine transmission. This is one of the reasons why the usefulness of typical dopamine antagonists (e.g. neuroleptics) in the treatment of alcohol dependence, is rather limited [13, 23].

Naltrexone and positive reinforcing effects of alcohol

Naltrexone can effectively interrupt the above described neurochemical mechanisms, and inhibit positive reinforcement associated with alcohol drinking (Figs. 1 and 2 *page 120*). It is important to note that opioid receptor antagonists act relatively selectively in CNS and do not block all the systems involved in rewarding action of natural and chemical stimuli. As far as the above described dopamine system is concerned, the effects of naltrexone are rather indirect and far from the potent effects of

neuroleptics [3, 11, 18, 25]. Naltrexone does not modulate, strongly or directly, the GABAergic, glutamatergic or noradrenergic transmission. Hence, naltrexone does not cause generalised anhedonia, while blocking the positive reinforcing effects of alcohol in patients susceptible to pro-opioid effects of alcohol [4, 18, 20].

Another explanation for the absence of generalised anhedonia after the administration of naltrexone is the relatively non-selective action of this compound within the opioid system alone. Naltrexone reduces the stimulation of the mi receptors, and to some extent the kappa receptors, which, given the varied functions of these receptors, has the potential to reduce reward deficits (Fig. 1 and 2).

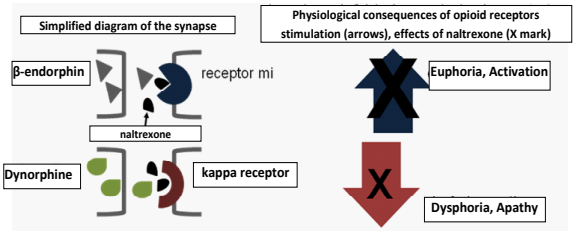

Fig. 1. β-endorphin – a natural, mi (μ) opioid receptors agonist, and dynorphin – a natural kappa (κ) opioid receptor agonist exert opposing effects on the reward system. Many reports support the fact that natural and chemical rewards, such as alcohol, relatively quickly activate (directly or indirectly) the mi receptors, and later the kappa receptors [5, 28]. The opioid receptor antagonist, naltrexone, reduces the mi receptor stimulation and to some extent the kappa receptors as well [25, 26]. This may translate into blocking conditioned opioid system stimulation induced by conditioned stimuli and into blocking unconditioned stimulation of the opioid system induced by alcohol. Naltrexone may also limit dysphoria induced by interruption of alcohol consumption (kappa receptor blockade) [8, 25]. Antagonising the mi and kappa receptors may explain why naltrexone inhibits craving caused by conditioned stimuli and the unconditioned effects of alcohol, reduces craving induced by negative emotional states, limits the rewarding effects of alcohol, reduces drinking, and ultimately promotes abstinence [e.g. 6, 8, 20].

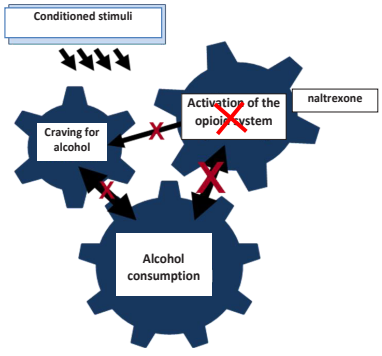

Fig. 2. A simplified model of positive reinforcing effects of alcohol during a drinking episode, taking into account the role of the CNS opioids. Stimuli inducing craving for alcohol (e.g. conditioned stimuli, stress) lead to initiation of drinking, inter alia, by reflex activation of the opioid system. Consumed alcohol produces an even stronger activation of the endogenous opioid system and increases craving. Therefore, the bold arrows are bidirectional. By blocking the mi opioid receptors, naltrexone inhibits the opioid transmission, reduces the initial, conditioned phase of the opioid system activation and promotes abstinence. By inhibiting activation of the opioid system induced by the consumption of alcohol, naltrexone lessens further drinking and reduces the risk of transition from a lapse to relapse [3, 8, 9, 10, 18, 20].

As already mentioned, single doses of alcohol activate – indirectly through the release of β-endorphin – mi opioid receptors. On the other hand, chronic alcohol use can lead to a reduction in sensitivity and a kind of tolerance of the mi receptors, and,

quite interestingly, *hypersensitivity* of the kappa receptors. Sensitization of the kappa receptors is thought to be typical to states appearing after quick withdrawal of alcohol, following its chronic use [25, 28]. It therefore appears that the reduction of kappa receptors activation by opioid receptors antagonists, could translate into additional therapeutic benefits.

In conclusion, to the extent that blockade of the mi receptors reduces the craving for alcohol, alcohol consumption and the positive subjective experience of drinking, the kappa receptor blockade can probably reduce relapses associated with dysphoria induced by alcohol withdrawal [3, 9, 20, 25]. Figure 1 shows the effects of physiological arousal of the mi and kappa receptors and the effects of naltrexone [11, 19, 23], while Fig. 2 shows a simple model of alcohol-induced positive reinforcement during a drinking episode [1, 3, 15, 17, 20].

Naltrexone in the treatment of alcohol dependence

Considering the behavioural mechanisms of opioid receptor antagonists, including naltrexone, it is worthwhile noting that these drugs may reduce positive subjective experiences related to drinking, conditioned and unconditioned component of alcohol craving (Fig. 2), and promote abstinence [6, 9, 17, 20]. This latter effect, i.e., maintaining total abstinence, is less well documented in clinical trials with naltrexone [17, 20, 23] (acamprosate is the drug, which mainly increases abstinence and reduces consumption to a lesser extent [29].)

From a practical point of view, it is an interesting and important issue that naltrexone does not alter the taste of ethanol, nor does it toxically react with alcohol as disulfiram does, and has no addictive potential like the opioid receptors agonists. It appears that its effectiveness depends on blocking the activity of the CNS (not peripheral) opioid receptors located in specific limbic structures (e.g. nucleus accumbens septi) [13, 19, 25]. There are therefore a number of theoretical and practical reasons to assume that naltrexone therapy can bring about the best results in patients who feel strongly rewarded by consuming alcohol - through the activation of the opioid system [3, 20, 23]. Unfortunately, appropriate markers have not been designed to allow prediction of favourable or unfavourable response to naltrexone treatment in everyday clinical practice [1, 15]. Two decades of clinical research have allowed to confirm that naltrexone may reduce the overall consumption of alcohol, consumption of alcohol during a single episode (per occasion), and limit the number of days during which alcohol is consumed in large and potentially harmful amounts (usually defined as $\geq$ 5 standard drinks for men, $\geq$ 4 standard drinks for women; i.e. heavy drinking days, HDD) [10, 11, 17, 20, 22].

These findings are well summarised in the meta-analysis published in 2010 by The Cochrane Collaboration [17] covering 50 studies on the use of naltrexone in the treatment of alcohol dependence. The studies included in the meta-analysis involved more than 7 700 patients. In most key studies the drug was administered at the dose of 50 mg once a day. In most of the cases, the duration of the observation was three months.

The use of naltrexone resulted in a significant 17-percent reduction in the risk of relapse to heavy drinking (≥4/≥5 standard drinks per day). Furthermore, administration of the drug led to a 4% reduction in the number of days during which alcohol was consumed, a reduction in the so-called HDD by about 3%, and a reduction of the amount of alcohol consumed per an occasion – by approximately 11 grams of pure ethanol – i.e. slightly more than one standard drink. Also an improvement in the liver function parameters (GGT levels decline) was observed. Naltrexone prolonged total abstinence, nevertheless this effect did not reach the statistical significance. It should be noted that the above presented average results, though important from a perspective of evidence based medicine (EBM), do not fully reflect the clinical reality in which some patients respond very well to treatment with naltrexone, while some of them seem to hardly benefit from the treatment [4, 15, 17].

The most important side effects associated with the use of naltrexone included gastrointestinal disturbances (nausea, abdominal pain, loss of appetite), fatigue, insomnia at night and drowsiness during the day. Importantly, the safety profile of the drug was judged to be satisfactory, and the drug's use in the treatment of alcohol dependence summarized as "safe" [17]. It is worthwhile recalling that naltrexone, as any other opioid receptor blocker, interacts with opioid agonists (e.g., fentanyl, morphine, heroin). This interaction may bear clinical importance for patients treated with opioid analgesics or patients addicted to opioid drugs. Administering naltrexone to patients chronically taking such compounds can lead to withdrawal symptoms [18].

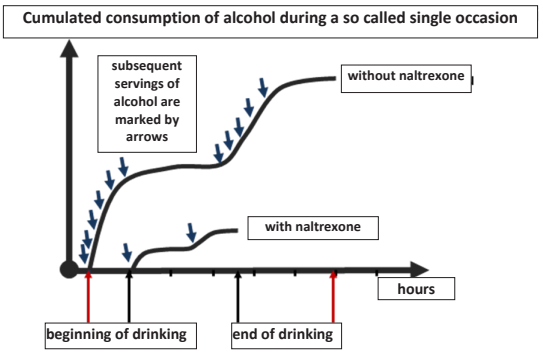

Fig. 3. Possible effects of naltrexone on alcohol consumption during an occasion lasting for several hours in a patient well responding to treatment. Naltrexone may delay the initiation of drinking, reduce the intensity of drinking, accelerate the end of a drinking episode (black, long arrows at the bottom of the figure) and prevent transition from a lapse to relapse [15, 20, 23, 26].

Summary

- Several decades of preclinical and clinical studies have revealed that the activity of the central opioid system is associated with craving for alcohol, rewarding effects of alcohol and binge drinking episodes. This is a direct justification for the

use of opioid receptors antagonists, such as naltrexone, in the treatment of alcohol dependence [3, 9, 10, 20, 23].

- Naltrexone has shown – as documented by numerous preclinical and clinical studies - beneficial effects, including reducing the craving for alcohol, limiting the amount of alcohol consumed per occasion and reduction in HDD [9, 10, 15, 17]. The effects of the drug on maintaining abstinence appear to be slightly weaker, though observed in some studies [4].
- Pharmacological effects of naltrexone make it different from disulfiram and acamprosate, both in terms of the mechanism of action as well as the clinical effects. Therefore, the available range of anti-alcohol drugs allows for individual selection of pharmacotherapy to suit patients' individual needs [4, 15].
- The use of naltrexone should be combined with psychotherapeutic intervention, in particular cognitive-behavioural therapy targeted to identify stimuli favouring relapse and coping in high-risk situations [4, 15, 17].

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Author's address:

Przemysław Bieńkowski
Institute of Psychiatry and Neurology
Sobieskiego Street 9
02-957 Warszawa

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