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Review

Naltrexone: A review of existing sustained drug delivery systems and emerging nano-based systems

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ABSTRACT

Narcotic antagonists such as naltrexone (NTX) have shown some efficiency in the treatment of both opiate addiction and alcohol dependence. A few review articles have focused on clinical findings and pharmacogenetics of NTX, advantages and limitations of sustained release systems as well as pharmacological studies of NTX depot formulations for the treatment of alcohol and opioid dependency. To date, three NTX implant systems have been developed and tested in humans. In this review, we summarize the latest clinical data on commercially available injectable and implantable NTX-sustained release systems and discuss their safety and tolerability aspects. Emphasis is also laid on recent developments in the area of nanodrug delivery such as NTX-loaded micelles and nanogels as well as related research avenues. Due to their ability to increase the therapeutic index and to improve the selectivity of drugs (targeted delivery), nanodrug delivery systems are considered as promising sustainable drug carriers for NTX in addressing opiate and alcohol dependence.

Contents

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1. Introduction

Treatment options for heroin addiction has long been dependent on three main alternatives namely detoxification, opioid agonist (*i.e.* methadone) and partial agonists (*i.e.* buprenorphine) maintenance treatment, and oral NTX. Detoxification followed by long-term residential treatment was found to cause some reduction in drug use but suffered from problems such as lack of retention in treatment and risk of overdose upon discharge [1]. Opioid maintenance treatment (OMT) involves the administration of opioid agonist medications such as methadone, buprenorphine and medically dispensed heroin under supervision [2]. OMT has been effective in decreasing mortality rates, morbidity and drug-related criminal activity. However, dropout rates remain quite high during the initial months of treatment.

As regards alcohol abuse, detoxification, non-pharmacological (psychosocial) treatment methods and pharmacotherapy have not been very effective. Disulfiram (Antabuse®), Naltrexone (Revia®), and calcium acetylhomotaurinate (Acamprosate®) are the three major oral pharmacotherapies used in the treatment of alcoholism. Disulfiram is a deterrent medication and makes its ingestion unpleasant. Acamprosate®, a glutamate antagonist has been found promising in the treatment of alcoholics [3,4] but present limitations. For some patients, combination therapy with NTX or disulfiram have proved to be effective [5].

The development of long-acting depot formulations of NTX has led to improved results such as increased bioavailability and efficacy of treatment and is considered as a solution to the problem of non-compliance and extensive first pass metabolism associated with oral NTX. This has been summarized in two excellent review papers [6,7]. In their review, Lobmaier et al. [6] emphasized on NTX depot formulations for opioid and alcohol dependence, discussing the mode of administration, the pharmacokinetic properties, safety and tolerability of the systems. The authors concluded on the need for further research on NTX to effectively block clinically relevant doses of heroin. Krupitsky et al. [7] summarized the effectiveness and safety of long-acting sustained release injectable and implantable formulations of NTX for heroin dependence. The authors concluded on improved tolerability and effectiveness of long-acting sustained-release NTX systems compared to oral NTX. They also mention that studies comparing the injectable formulation with oral NTX are required. In both reviews, the delivery systems are limited to NTX-loaded polymer-based microspheres.

This article reviews existing naltrexone delivery systems and their limitations and presents benefits of emerging nano-based delivery systems. In the first part of the review, we present the mechanism of action of NTX and its interest as a substitute for methadone followed by an in-depth analysis of commercially available NTX formulations with more recent references based on clinical trials through 2011 to 2013. We have summarized safety and tolerability aspects of extended-release formulations to ease access to information. We also stress on new nano-based NTX developments such as block copolymer micelles and cross-linked nanogels that attract a lot of interest and opens up new perspectives for research.

2. Current treatment against opiates and alcohol dependency

Opiates generally refer to any of the narcotic opioid alkaloids found as natural products in the opium poppy plant, *Papaversomniferum* [8]. Few examples of opiates include heroin and codeine. Opiate drugs act both in the central and peripheral nervous systems and opiate-dependent patients show impairment in brain functioning [9,10]. Agonists and partial agonists such as methadone and buprenorphine respectively, and antagonists such as NTX have been used in the management of opioid dependence.

2.1. Agonist therapy: methadone and associated problems

Methadone was first developed in Germany in 1937. However, its use as a substitute for heroin in the management of heroin dependence was not until 1964 [11]. Methadone has cross tolerance with other opioid compounds such as heroin, morphine and codeine and can therefore be used as a chemical replacement for the illicit opioid. The treatment of opioid addicts with methadone involves an initial methadone maintenance program (MMT). MMT is the most widely used opioid substitution program for the management of heroin dependence and its clinical efficacy has been repeatedly shown by several studies [12]. Being long acting, methadone should be administered only once daily as opposed to heroin which requires twice or thrice daily dose administration. Its oral route of administration substantially reduces the potential risks of spreading Hepatitis C or HIV. However, methadone therapy has few limitations.

Methadone therapy is associated with a number of problems. Due to its full μ opiate receptor agonist action, there is no limit to the level of respiratory depression or sedation that methadone can induce. As a result, methadone overdose can be lethal, with risk being particularly high during the induction period [13]. The combination of methadone with other opioid drugs, benzodiazepines or alcohol increases the risks of sudden cardiac death [14] and death by anoxic brain injury with pulmonary edema secondary to respiratory depression [15]. Methadone may increase the likelihood of QT interval prolongation [16] and may be associated with torsades de pointes [17] that can be fatal.

As methadone has a long half-life, coming off methadone is associated with a longer period of opioid withdrawal symptoms than when coming off heroin. This results in a significant degree of discomfort in patients who attempt to stop methadone. Methadone is a corrective but not a curative treatment for opioid addiction. Newer treatments with opioid antagonists like long acting NTX formulations need to be explored further as the initial results look promising.

2.2. Partial agonist therapy: buprenorphine and associated problems

Buprenorphine is a partial μ agonist and κ opiate receptor antagonist. It is also used in the treatment of opioid dependence and has several potential benefits over MMT. It is less sedating than methadone due to the fact that it is a partial μ receptor agonist. Also, it is associated with lower overdose risk since it rarely causes respiratory depression when used alone [18]. One way of reducing the abuse liability of buprenorphine [19] without affecting its bioavailability has been *via* the addition of naloxone hydrochloride to buprenorphine in a ratio of 1:4 (Suboxone, Reckitt Benckiser) [20]. Suboxone® was approved in April 2006 by the Therapeutics Goods Administration (TGA), and is now largely replacing buprenorphine hydrochloride (Subutex®) as the principal formulation for ambulatory clinical treatment of opioid dependence. Buprenorphine is available in different forms as summarized in Table 1.

New dosage forms of buprenorphine include transdermal patches [22], orodispersible or mucoadhesive buccal films [23]. The transdermal buprenorphine patch, Transtec®, first launched in 2001 uses a matrix technology whereby buprenorphine is homogeneously incorporated in a solid polymer matrix patch [22]. Transdermal buprenorphine patches are available in three different dosages with total loading doses of 20 mg, 30 mg, and 40 mg which release the drug at a controlled rate of 35 μg/h, 52.5 μg/h and 70 μg/h respectively [22]. BUNAVAIL™ is the first and only buccal formulation of buprenorphine and naloxone [24]. A New Drug Application (NDA) was submitted to the Food and Drug Administration (FDA) in 2013 and is currently under review.

A consensus on the relative superiority of buprenorphine over MMT remains elusive. Many studies reveal no significant differences between the treatments [25]. Others report significantly higher rates of retention in treatment, and abstinence from, or reduction in illicit opiate consumption among buprenorphine patients than among MMT patients [26]. A few studies described more favorable outcomes for MMT than