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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

Table 1
Different forms of buprenorphine.

Trade name	Dosage form	References
Subutex® (buprenorphine)	Sublingual tablet (2 mg and 8 mg)	[21]
Suboxone® (buprenorphine/naloxone)	Sublingual film (4 mg buprenorphine/1 mg naloxone and 12 mg buprenorphine/2.5 mg naloxone)	
Zubsolv® (buprenorphine/naloxone)	Sublingual tablet (2 mg buprenorphine/0.5 mg naloxone and 8 mg buprenorphine/2 mg naloxone)	
Transtec®	Transdermal	[22]
Butrans®	Transdermal (delivering 5, 10 or 20 g/h)	[23]
Norspan ®	Transdermal (delivering 5, 10 or 20 g/h)	

for buprenorphine in terms of retention, abstinence for at least three weeks, opioid-free urine [27], and cost-effectiveness [28]. Nevertheless, overall pharmacokinetic features suggest that buprenorphine is safer than MMT, with respect to its reduced risk of respiratory depression, withdrawal symptoms, and accidental opioid overdose deaths [29] and reduced potential for abuse [30].

2.3. Antagonist therapy: naltrexone and its mechanism of action

Narcotic antagonists such as NTX, have been found useful in the treatment of both opiate addiction and alcohol dependency [31,32]. NTX has a chemical structure similar to opiates and can occupy the body's opiate receptors in preference to opiates. The ability of NTX to effectively antagonize heroin use is unequivocal [33,34]. Studies have reported serum NTX levels of 2.8 ng/ml as being effective in blocking 500 mg of snorted pure pharmaceutical diamorphine [35], serum naltrexone levels >2 ng/ml [34–38] as being effective in blocking the effects of 25 mg intravenously administered heroin, and others have reported plasma levels of less than 1 ng/ml as being capable of antagonizing the effects of 15 mg morphine [39].

NTX is an opioid receptor antagonist that blocks the reinforcing effects of opioids and reduces alcohol consumption and craving. Historically, N-allylnorcodeine was the first opioid antagonist-like molecule developed in 1915. It acted by blocking the respiratory-depressant effects of morphine and heroin. In the 1940s, nalorphine was the first reported opioid antagonist but was found to cause dysphoria, discouraging its use in the treatment of opioid intoxication and overdose. Naloxone was then developed in 1960 as a less toxic antagonist. It did not cause any dysphoria but suffered from short duration of action and poor oral bioavailability. To circumvent these disadvantages, NTX was developed in 1963 by Endo Laboratories, which was later acquired by DuPont. It is generally synthesized from thebaine (an opiate alkaloid) [40] and was found to have better oral bioavailability, a longer duration of action and twice as potent as naloxone. Naltrexone hydrochloride is freely soluble in water, slightly soluble in ethanol (approximately 96%), and practically insoluble in methylene chloride [41]. It is a BCS Class IV drug *i.e.* it has low solubility and low permeability.

Table 2 gives a summary of the pharmacokinetic data of NTX. NTX is FDA-approved for the treatment of alcoholism or opioid addiction in the form of commercially available oral tablets *e.g.* Trexan®, Revia®, Depade® or the long-acting, high-dose depot form Vivitrol® for intramuscular injection.

Table 2
Pharmacokinetic data of NTX [37,42].

	Naltrexone
Chemical formula	$C_{20}H_{23}NO_4$
Oral bioavailability	Up to 40%
Metabolism	Hepatic
Peak concentration	1–2 h
Half-life	Up to 14 h (oral)
Duration of action	Up to 24+ h
Elimination	Hepatic metabolism and renal excretion
Peak plasma level	1 to 2 ng/ml

Studies have revealed that the mesolimbic dopamine system is the prime target of addictive drugs. This system originates in the ventral tegmental area (VTA) of the brain (Scheme 1). Most projection neurons of the VTA are dopamine-producing neurons. GABA interneurons suppress dopamine cell firing resulting in reduced dopamine release. Opioids block the inhibitory control exerted by these neurons over the VTA dopamine cell bodies resulting in increased VTA dopamine activity, thus enhancing brain-reward (reinforcement circuit in the human brain) and inducing drug-taking behavior and possibly drug-craving. Each addictive drug has a specific molecular target which engages a distinct cellular mechanism. The main molecular receptors of opioids are μ-OR G_{io} protein-coupled receptors.

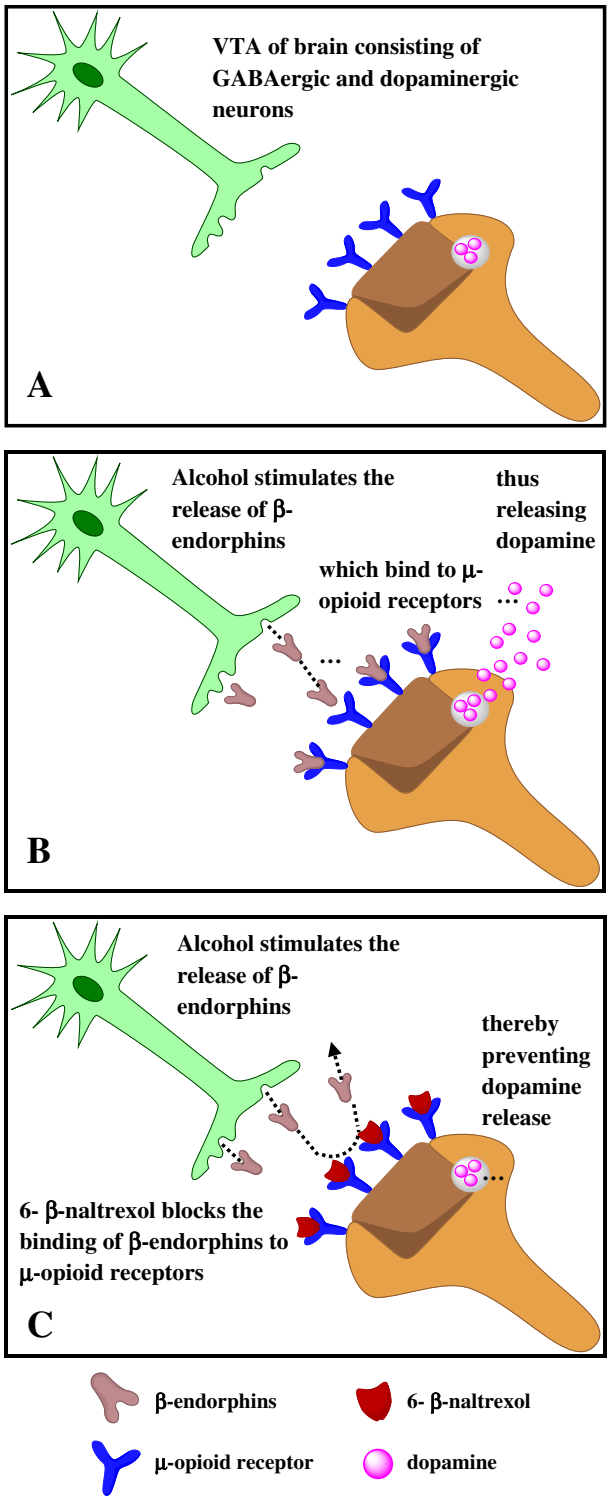
NTX acts by blocking the μ-opiate receptors, thus reducing craving. The precise mechanism for craving reduction has not been determined yet, but it is likely that NTX causes antagonism of opioid pathways to the nucleus accumbens, thereby reducing the total amount of dopamine released (Scheme 1). In addition, opioid antagonists like NTX influences other biological systems such as G-receptor second messenger systems [43], immune system [44] and the HPA axis [45]. NTX is metabolized in the liver into a variety of metabolites, with 6-β-naltrexol being the metabolite useful in treating drug abuse (Scheme 2). 6-β-naltrexol is believed to act as a competitive antagonist at opioid receptors. Cytochrome P450 enzymes, which are involved in the metabolism of methadone or buprenorphine do not play a role in NTX metabolism. NTX is largely metabolized by the aldo-ketoreductase family of enzymes (AKR1C1, 1C2 and 1C4) [46] with AKR1C4 being the most efficient [47]. It is believed that a polymorphism of the AKR1C4 enzyme is responsible for inter-individual variability in 6-β-naltrexol levels and could be used to explain the efficacy of and compliance with NTX treatment [46].

Due to its higher potency compared to naloxone and cyclazocine, NTX is considered as the most promising narcotic antagonist used for the treatment of narcotic addiction [48,49]. A minimum plasma level of NTX of 1 ng/ml is required for blocking clinically relevant doses (*e.g.* 25 mg) of intravenously administered heroin [50]. Evaluation of a program where cognitive behavioral therapy (CBT) and/or NTX were used over 12 weeks showed that addition of NTX significantly improved the abstinence rate (36.1% CBT against 62.6% CBT + NTX) [51].

However, oral NTX (Revia® tablets) has been associated with high early dropout rates. It was shown that 37% of patients discontinue daily oral NTX by 12 weeks [52] and more than 80% discontinue use by 6 months [53]. As demonstrated by several studies, compliance is critical for the efficacy of NTX [54]. Moreover, orally administered NTX has poor bioavailability due to high hepatic metabolism (98%) and a wide fluctuation in drug plasma concentration occurs with orally administered NTX [55]. Indeed, a review of the effectiveness of oral naltrexone maintenance for the treatment of opioid dependence concluded that there was insufficient evidence to justify the use of NTX in maintenance treatment of opioid addicts [56].

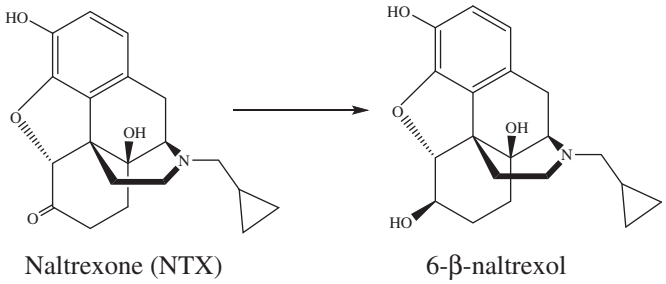
3. Limitations of oral NTX

As mentioned earlier, NTX is available commercially as tablets for oral administration. However, they have several pharmacotherapeutic limitations. First of all, more than 98% of the drug is metabolized in the liver and very small amount reaches the brain. Due



Scheme 1. Schematic representation of interplay between GABAergic and dopaminergic neurons in (A) absence of drug of abuse and its antagonist, (B) presence of drug of abuse only and (C) presence of both drug of abuse and its antagonist.

to extensive first pass metabolism, the concentration of naltrexone and the active metabolite, 6-β-naltrexol peaks within the first hour after oral dosing, followed by a steady decline each day during treatment [57]. This explains the need for the development of a system whereby NTX bypasses the liver *i.e.* an injectable long-acting drug delivery system. Such a system will enable the maintenance of a constant and predictable drug plasma concentration. According to a study conducted



Scheme 2. Metabolism of NTX to 6-β-naltrexol.

by Verebey et al. [55] among alcoholics, drug plasma levels fluctuates much with orally administered NTX. In fact, a 100 mg naltrexone dose provided 96%, 86.5% and 46.6% blockade at 24 h, 48 h and 72 h respectively. Moreover, the use of oral NTX places the onus on the patients as to whether to take the medications or not and very often, they do not comply with the required frequency. Studies have also shown that a comparatively low proportion of patients choose to start NTX treatment [58]. Among those who do, many drop out early; one quarter after a few days [33] and as many as half in the first few weeks of treatment [59]. This is a major problem given that several studies have demonstrated that missing even a few doses of NTX could lead to full relapse into opioid use and discontinuation of the treatment, despite intensive clinical interventions [54,60].

4. Drug delivery: basic principles

Drug delivery systems (DDS) may be differentiated according to the way the drug is administered or released. They may be administered through oral or parenteral (intravenous, intramuscular, subcutaneous, intradermal or intraperitoneal) routes [61].

DDS can broadly be classified as immediate release and modified release dosage forms. Modified-release systems can be further divided into delayed-, extended- and targeted-release systems. Furthermore, extended-release systems can be divided into sustained- and controlled release systems [61] (Fig. 1).

Sustained release systems maintain the rate of drug release over a sustained period of time [61]. Sustained release systems may be either in the form of reservoir or matrix systems. Reservoir systems often follow a zero-order kinetics (linear release as a function of time) while matrix systems often follow a linear release as a function of the square root of time. Sustained release systems offer several advantages such as reduced fluctuations in drug concentrations, and reduced total dose. Also, the patient does not require taking the drug frequently and therefore resolves the issue of non-compliance.

Controlled-release systems are different from sustained-release ones [61]. They are designed to maintain specific plasma concentrations, independent of the biological environment of the application site [61,62]. Another major difference is that sustained-release forms are often restricted to oral dosage forms. On the other hand, controlled-release systems are used in a variety of administration routes, including transdermal, oral and vaginal administration [61].

Release from oral NTX tablets may be termed as a burst release, resulting in fluctuating plasma concentrations during the day (Fig. 2). NTX concentration peaks within the first hour of oral dosing followed by a fairly rapid decline in plasma levels to below the minimum therapeutic levels (2 ng/ml) within 8 h of dosing [63]. The use of a sustained release NTX formulation will result in slow NTX release, avoiding the peaks and troughs associated with daily drug administration, while maintaining continuous therapeutic plasma levels for an extended time frame. This "smoothing out" of drug levels in the blood may decrease the possibility of occurrence of adverse events associated with peaks, and improve efficacy by avoiding drug concentration troughs.

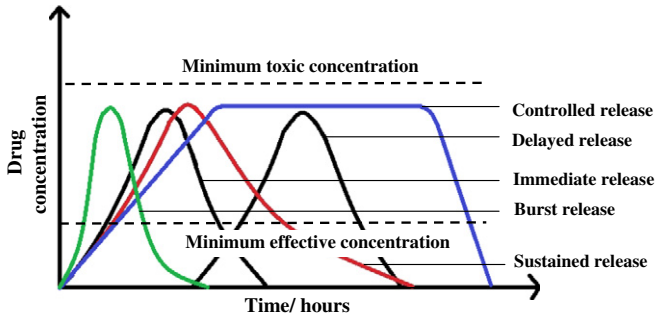


Fig. 1. Drug release kinetics.

Drug release may be modeled using different models as shown in Table 3 [64]. The R^2 values are used to check which model best fits the release system.

Polymer based drug delivery systems may be categorized as diffusion-controlled, solvent-activated (swelling or osmotically controlled), chemically controlled or externally-triggered (*e.g.* pH, temperature) [65].

Immediate-release, modified-release, extended-release and delayed-release have been defined by the FDA. However, no definitions have been provided for targeted or controlled release [61].

Barzegar-Jalali et al. reported on a general model applicable to multi-mechanistic release from nanoparticles (Eq. (6)) [66]. Parameters obtained from this model may be used to compare different delivery systems of a given drug as well as correlating with bioavailability data. Indeed, the release half life, $t_{50\%}$ can be used to compare release rates of different systems. The values of the different parameters obtained for NTX-loaded hydrolyzable crosslinked nanoparticles (using Eq. (6)) are given in Table 4. The $t_{50\%}$ value obtained for the more hydrophobic PEO–MMA copolymer (1:4) suggests a more sustained release compared to the PEO–MMA copolymer (1:1).

$$\frac{1}{F} - 1 = \frac{m}{t^b} \tag{6}$$

The use of kinetic models helps to elucidate release mechanisms, which can in turn be useful to control drug release. The mathematical models discussed above can help optimize existing systems and ultimately design a polymer-based therapeutic system with the drug released at the required rate and concentration.

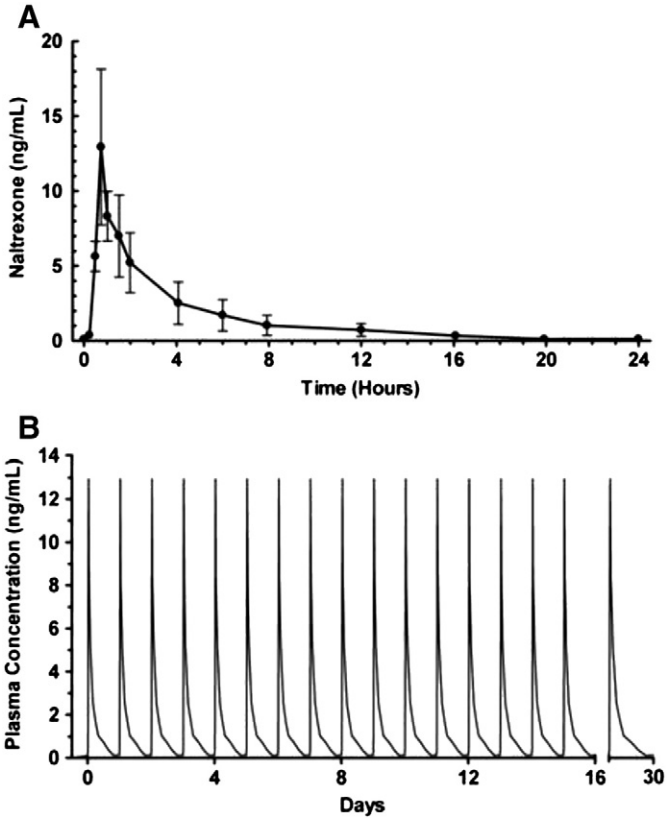


Fig. 2. (A) Typical profile of plasma NTX levels over 24 h following a 50 mg oral dose in humans. (B) Simulation of the daily fluctuations in plasma levels of NTX over the course of a month, assuming the patient adheres to the daily dosing of oral NTX. Reprinted with permission from [63].

Table 3
Kinetic models used for analysis of drug release data.

Model Name	Model	Overall mean percent error
Zero order	$M_t = M_0 + k_0 t$	18.28
First order	$\log C_t = \log C_0 - Kt/2.303$	16.41
Higuchi	$M_t = K_H t^{1/2}$	10.65
Hixson–Crowwell	$M_0^{1/3} - M_t^{1/3} = \kappa t$	26.63
Power law	$\ln F = \ln K_p + p \ln t$	7.66

M_t: amount of drug dissolved in time t.
M_0: initial amount of drug in the solution.
k_0: zero-order release constant.
C_t: concentration of drug dissolved in time t.
C_0: initial concentration of drug.
K: first order rate constant.
t: time.
K_H: Higuchi dissolution constant.
κ: constant incorporating the surface-volume relation.
F: fraction of drug released at time t.
p, K_p : parameters of the model.

5. Sustained-release NTX formulations

An alternative NTX maintenance delivery against the problem of non-compliance involves injection or surgical insertion of a sustained release preparation of NTX, avoiding the gastro-intestinal route. This removes the need for daily oral NTX.

5.1. Sub-cutaneous formulations

The concept of sustained release preparations of NTX is not new. Beginning in the mid-1970s, a number of depot formulations of NTX were developed. While showing promising NTX release patterns, and being of 'likely biodegradable materials', most had unacceptable tissue compatibility. For example, Chiang et al. [67] conducted one of the early studies of sustained release NTX in normal, healthy volunteers implanted subcutaneously with naltrexone-copolymer (90% L-lactic acid and 10% glycolic acid) beads. Following an initial burst of release, this formulation yielded relatively constant plasma levels of NTX (0.3–0.5 ng/ml) for up to 1 month. Data indicated that this NTX preparation had unacceptable levels of biocompatibility, with two of the three human subjects implanted with the naltrexone-copolymer (90% L-lactic acid and 10% glycolic acid) beads having

Table 4
Summary of parameters obtained for NTX release using the reciprocal powered method [66].

Nanosystem	N[a]	R^2	E	m	b	$t_{50\%}$ (h)
PEO–MMA copolymer (1:1)	6	0.895	3.0	1.967	0.603	3.1
PEO–MMA copolymer (1:4)	17	0.650	10.5	3.559	0.431	19.0

N: number of data in each set.
E: percent error.
F: fraction of drug released in time t.
m, b: parameters of the model.

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