Substance Abuse: Research and Treatment

REVIEW

Epidemiologic and Molecular Pathophysiology of Chronic Opioid Dependence and the Place of Naltrexone Extended-Release Formulations in its Clinical Management

Albert Stuart Reece

School of Psychiatry and Clinical Neurosciences, University of Western Australia.
Corresponding author email: sreece@bigpond.net.au

Abstract: Naltrexone implants and depot injections (NI) are a novel form of treatment for opiate dependence (OD). Major questions relate to their absolute and relative efficacy and safety. Opportunely, six recent clinical trial data from several continents have uniformly provided dramatic evidence of the potent, dose-related and highly significant efficacy of NI, with minimal or manageable accompanying toxicity and safety concerns. The opiate-free lifestyle is attained significantly more often with NI adjusted O.R. = 6.00 (95% C.I. 3.86–9.50), $P < 10^{-10}$. Other drug use and drug craving are also rapidly reduced. The optimum manner in which to commence NI remains to be established. Of particular relevance is the relative safety of NI compared to the chronic opiate agonists (COA) usually employed, as the long-term toxicity of COA is only just being elucidated. Large population-based studies have found elevated rates of cardiovascular disease, six cancers, liver and respiratory disease, and all-cause mortality in COA. Whilst opiates have been shown to trigger numerous molecular pathways, the most interesting is the demonstration that the opiate morphinan's nucleus binds to the endotoxin groove of the TLR4-MD2 heterodimer. This has the effect of triggering a low grade endotoxaemic-like state, which over time may account for these protean clinical findings, an effect which is reversed by opiate antagonists. This emerging evidence suggests an exciting new treatment paradigm for OD and a corresponding increase in the role of NI in treatment.

Keywords: naltrexone implant, extended release naltrexone, aging, immunostimulation, immunosuppression, pathophysiology, toxicopathology, chronic opiate agonism

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Overview and Review Methodology

The gradual introduction of extended release naltrexone (EX-NTX) preparations into the clinical treatment paradigm, which for over fifty years now has primarily been centered on agonist treatments, has generated much excitement and more than a little controversy. Two key issues surround the assessment and review of the potential role of EX-NTX in the clinic. These relate firstly to the *absolute* features of EX-NTX as relates to its objective safety and efficacy. The second issue, which is actually more pertinent to its widespread clinical adoption, relates to its *relative* place in the treatment armamentarium in comparison with the other major treatment options currently widely available. To understand the present and emerging place of naltrexone in the clinic, it is important to have some understanding of both the absolute and relative place of EX-NTX.

Addressing these two questions requires very different methodological approaches. There are relatively few randomized clinical trials of EX-NTX, which can be summarized and reviewed to provide a formal answer to the questions relating to absolute safety, efficacy and other concerns. Clinical trial results represent the major publications relating to these subjects. Clinical trials were included in this review by searching the terms "extended release naltrexone" (50 papers identified) "injectable naltrexone" (23 papers identified) and naltrexone implants (153 papers identified) in the PubMed literature database, and then searching through identified papers from there. Six randomized trials of depot or injectable naltrexone were identified. Such a review is presented, including a meta-analysis. However, both the conceptual context and the clinical treatment environment demand that at least some consideration of the relative toxicity of treatments involving chronic opiate agonism be considered. Procedurally this is a very different undertaking because the literature relating to the clinical and molecular toxicology and mechanism of action of opiates is so voluminous and necessarily complex. This part of the review, which sets the scene for the discussion of the role of EX-NTX, is undertaken in a more narrative format that seeks to extract some of the major publications in the area and highlight what are seen as some of the most important conceptual advances in the field.

Introductory and historical remarks

Opiate dependence (OD), arising from the treatment of benign chronic pain conditions, from recreational drug use, and from the clinical treatment of opiate dependence, is a problem of increasing public health proportions both by way of overdose-related deaths and by its role in the spread of blood borne viruses, particularly HIV and hepatitis B and C. It is also well known to be related to crime, recidivism, numerous social and economic disadvantages, congenital malformations including neurological and learning deficits, and most recently, cancer.

The clinical treatment of this condition began in earnest in New York as a result of a crisis in escalating drug use in some returning Vietnam War Veterans.[1] The most suitable available agent at the time was considered to be methadone. From this historical basis, opiate substitution treatment grew across the world until the present date, where it is available in 70 countries.[2] In 1989, major clinical trials were conducted with buprenorphine, which is also widely used now in many opiate replacement programs. As with any pharmacological agents, these agents themselves are associated with adverse events, with methadone implicated in many polydrug overdose deaths, and buprenorphine injecting becoming a bigger problem than pure opiate agonist dependence in many nations, including Russia, Georgia and Mauritius.[2] Chronic opiate agonist treatment has been shown to be associated with a two to four fold reduction in death rates and lower HIV infections rates,[3] but on the other hand to also greatly prolong the duration of the opiate dependency syndrome by at least a factor of five.[4] Methadone, alone or in combination, was associated with 957 deaths in Australia for the period between 1997 and 2005, according to ABS custom data.

Moreover, a basic tension exists between fundamental treatment goals, drug-dependent persons, and their treating industry. It has been repeatedly shown that at least 80% of drug-dependent patients seeking treatment wish to relinquish their drug dependency and achieve a normal drug-free lifestyle.[5] However, since the drug-free state is accompanied by a high relapse rate and characterized by many failed attempts to detoxify, and because the major medical treatment options available are themselves opiate agonists or partial agonists, there exists a fundamental mismatch and lack of synergy between delivery and treatment uptake.

Many patients, and the community at large, generally wish to find pharmacological freedom;[6] the industry offers "management" of the problem, which in practice implies maintenance of the dependency in a more manageable form. In recent times such maintenance treatments have been conceptualized within a harm reduction and harm minimization paradigm, which in many places are synonymous with drug liberalization policies and practices.

Naltrexone was first synthesized in Blumberg's laboratory in 1963 at Endo Laboratories.[7] It was derived from oxycodone by substituting the tertiary amine methyl group on the morphinan skeleton for a cyclopropane ring. Naltrexone was found to be a highly efficacious water soluble opiate-competitive antagonist, with an unusually high affinity for the μ-opiate receptor in the low nanomolar range, where it binds with 20 times the affinity of morphine.[8] When taken as directed it is highly effective at blocking the effects of opiates for 24 to 36 hours, and when used clinically, it prevents relapse to dependent drug use and overdose. It is not habit-forming and patients can cease use without effect at any time. It has no major side effects when used in the normally recommended doses.[9] On this basis clinical trials were conducted with the oral preparation in the 1970's, but compliance was quickly recognized as a major issue.[10] Amongst patients in whom compliance could be assured, such as professional people whose employment depended on their continued sobriety, parolees under legal supervision, and young people still living with their parents, excellent results were reported,[11–13] but this was not the general experience.[10] For this reason a pharmaceutical development project sponsored by NIDA began to consider the development of depot-implantable forms of naltrexone. As long ago as 1975 NIDA called for the further development of NI.[14] Indeed, in 1975 a system similar to that used presently, based on polylactide-polyglycolide co-polymers, as is used for absorbable sutures, was reported.[15,16] That project apparently faltered due to local tissue reactivity of the preparations employed.[17]

An injectable extended release form of naltrexone, Vivitrol (Alkermes), is available in the United States and was registered by the FDA in the USA for the treatment of opiate addiction in 2011. The implant releases over one month. Various implants are available in many countries, including the USA, Germany, Russia and China.[18] These were most often a compacted pellet of naltrexone in a magnesium stearate matrix and also usually act for one month. At one time such implants contained triamcinolone in order to reduce local tissue reactions. One such implant comes from the George Sherman pharmacy in New Jersey and is marketed in Russia as Prodetoxone.[12] This is the only registered NI in the world.[19] Two different Chinese implants are available, and are active for 5 and 10 months respectively. Since 2000 the "Go Medical" group in Perth has compounded naltrexone implants based on the polylactide-polyglycolide microsphere technology. Two randomized trials have been conducted using this device.[20,21] Versions of this implant are now available lasting twelve months and development is proceeding towards a version that will last 24 months. It is widely agreed that serum levels of 1–1 ng/mL of active naltrexone are required to effectively block opiate use. Pharmacokinetic data is available which shows that this occurs for the respective periods quoted for each device. Various other naltrexone implants are under development in the USA. Implants are sterilized by gamma irradiation.

The clinical manifestations of opiate dependence are protean, although many of them are not widely known. Numerous endocrinopathies, including hyperglycaemia and diabetes, immune stimulation and depression, atherosclerosis, chronic chest disease, six different cancers, coagulopathies, and some of the major characteristic stigmata of the human aging syndrome, including grey hair, chronic periodontitis, reduced stem cells, and cancer, have recently been described. Initially it is not immediately apparent why such diverse stigmata should be associated with OD. One of the most interesting developments in recent times is the demonstration that the morphinan nucleus of opioids binds (non-stereospecifically) directly to the endotoxin-binding groove of myeloid differentiation factor 2 (MD2), the extracellular binding partner of toll-like receptor 4 (TLR4), and the endotoxin pattern recognition receptor (PRR) located in the plasma membrane. Such a scenario of a subacute-on-chronic, low grade endotoxaemia-like syndrome would not only account for the numerous disparate clinical manifestations of opiate dependence, but also the various cellular and subcellular pathways which have been described as being activated by opiate agonism. Naltrexone reverses this activity.[22]

Opiates also act to tonically inhibit the cell cycle and stem cell division.[23] This is reversed by naltrexone. Opiates also cause or potentiate apoptosis in many experimental systems.[24] Clearly, the effect to inhibit the cell cycle would be exacerbated by the effect on apoptosis. Both would interact negatively with the above-mentioned immune activation.

The availability then of reliable long-acting naltrexone preparations with low intrinsic tissue-reactivity, shown in various clinical trials to be both safe and highly efficacious against the full gamut of addictions, provides for the first time the opportunity to align the major treatment objectives. Opiate dependent patients would see improved health status and the attainment of a drug-free lifestyle, the community's major goal for its drug-dependent members would be realized, and at last a major alternative to the chronic opiate agonism which has for so long formed the mainstay of clinical pharmacotherapy would be achieved.

Mechanism of action

Whilst clinicians and researchers have studied the mechanism of action of opiates from the time of Claude Bernard in 1877[25] until and more recently since the modern era since the cloning and sequencing of the μ-opiate receptor in 1975,[26] recent developments show that we are as yet far from a complete understanding of the physiology of the opiate system either within the neuraxis or more generally throughout the organism.

It is important to have a better understanding of the nature of chronic opiate dependence to have some appreciation of *why* our patients might be encouraged to pursue a drug-free lifestyle. After five decades of strongly agonist based treatment, with its determinedly maintenance oriented stance, the complete formulation of the nature and conceptual basis for drug-free or antagonist-based treatment is so radically counter-paradigmatic as to require some detailed exploration of its rational scientific basis.

The effects of the levorotatory isomer of naltrexone in stereospecifically blocking the classical μ-, δ-, κ- and orphanin/nociceptin opiate receptors on neuronal and other cells is well established. It is believed that naltrexone binds non-competitively to these receptors in such a way that the receptors are ligated but not activated. Some of these receptors are internalized. In some experimental animals, receptor super-sensitization has been described whereby opiate blockade is accompanied from the synthesis of an increased number of opiate receptors.[27] Since many immune cells also carry these receptors, it is believed that naltrexone binds both within the CNS and also to immune, endothelial, and other cells throughout the organism that carry these receptors.

Hedonic appetitive stimulation

One particular group of neurons crucially important to the body's metabolism is the proopiomelanocortin (POMC) cells found in the arcuate nucleus of the hypothalamus. These neurons synthesize the large preproprotein precursor molecule proopiomelanocortin, which is a precursor of both the adrenocorticotrophic releasing hormone (ACTH) β-endorphin and the α-melanocyte stimulating hormone (αMSH). αMSH is the active anorexigenic neurotransmitter.

These cells are therefore referred to as melanocortergic and are anorexigenic. They counterbalance the neuropeptide-Y (NpY) orexigenic neurons also located in the arcuate nucleus in order to govern appetite and many appetitive behaviors.[28] As long ago as 2001 Cowley et al showed in Nature journal that the application of opioids to the POMC neurons hyperpolarized these neurons, from a mean resting potential of about –40 mV to about –60 mV, accompanied by a complete loss of the otherwise numerous spontaneous action potentials.[29] It therefore does not seem unreasonable to presume that opiate antagonists such as naltrexone would tend to both depolarize these anorexigenic neurons and increase their spontaneous and stimulated firing rate.

Table 1 reflects the results of a literature search performed on August 29, 2012 showing the number of papers cited in the PubMed database for several selected indications of naltrexone. Whilst the indications for alcohol abuse and opiate dependency are well known, it is noted that several other putative and prospective indications also exist. As indicated in the table, these therapeutic applications are noted to fall into four groups, namely chemical addictions, behavioral addictions, fertility and immune uses. From such a listing it becomes very clear that naltrexone must be exerting some profoundly anhedonic influence on the hypothalamic appetitive center, since it has been shown to reduce the use of virtually all drugs and most known behavioral addictions. Whilst some

Table 1. Clinical indications for naltrexone by numbers of PubMed citations.

Indication	References
Drugs of abuse	
Opioids	3688
Alcohol	1407
Cocaine	240
Benzodiazepines	172
Amphetamine	136
Tobacco	46
Cannabis	20
Behaviours	
Weight	463
Naltrexone/bupropion	66
Kleptomania	55
Gambling	32
Self-mutilation	24
Trichotillomania	7
Fertility	
PCOS	25
Infertility	13
Immune	337
Chronic fatigue	165
Fibromyalgia	62
Multiple sclerosis	11
Crohn's disease	6

non-specific effect mediated cerebrally via classical opiate receptors is often vaguely discussed, it appears more parsimonious to implicate the opioidergic melanocortin neurons of the appetite center known to pivotally control such mechanisms. Contrariwise, many surveys of agonist treated patients have shown very high rates of use of hedonic substances and behaviors including opiates, amphetamines, cocaine, cannabis, alcohol, tobacco and heroin. Risky sexual behaviors are also well known in this group. There is a large and well established literature on the effect of opiates in encouraging a low quality diet high in simple carbohydrates and saturated fats.[30–32] This mechanism has been described in detail.[33] These results have important implications because they imply that not all opioid pharmacotherapies are equivalent. Beyond simply the management of the opiate addiction itself, such data strongly point to the effect of opiate agonists and antagonists in encouraging other drug use and discouraging hedonic high risk behaviors respectively. Such findings clearly have far reaching law enforcement and public order implications.

With regard to the use of naltrexone in fertility, various authors note that the hypothalamus exerts tonic opioid-dependent inhibitory control over both the hypothalamic-adrenocortical and the hypothalamic-gonadal axes. This inhibitory action is clearly blocked by opiate antagonists.[34]

TLR4-Mediated central metabolic dysregulation

The importance of these neurons is greatly amplified even beyond this important role. These same hypothalamic neurons have now been implicated in systemic opiate-induced neuroinflammation. Indeed, it has been shown that opiate induced, toll-like receptor 4 (TLR4)-mediated cerebroinflammation can cause the hypertension, hyperlipidemias, obesity, and insulin resistance characteristic of the metabolic syndrome in mice, which is disrupted by knockout either of the POMC cells themselves, their TLR4 receptors, or their downstream signaling cascades.[35] Such studies imply that opiates increase many of the risk factors for degenerative disorders such as atherosclerosis and Alzheimer's dementia. Because hypothalamic inflammation is coupled to systemic inflammation both by sympatho-adrenomedullary stimulation and by hypothalamic-adrenocortical pathways, such inflammatory disorders are also likely to be stimulated by central pathways, in addition to the peripheral pro-inflammatory, pro-senescence actions of opiates described below.

The toll receptor was first identified in drosophila, where it was found to be implicated in dorso-ventral patterning and the formation of invaginated pit primordial in areas such as the mouth, larynx and anogenital region.[36,37] This is reminiscent of the known role of TLR-induced cytokines, particularly TNFα, as a major structural determinant of brain formation, which is relevant in key developmental stages such as in utero and in the second and third decade of life, when brain formation is also known to occur.[38–40]

Ten of the 13 described toll-like receptors (TLRs) are found in man. They are highly conserved pattern recognition receptors which powerfully stimulate the innate immune system as an early response system in dealing with invading pathogens (pathogen associated molecular patterns, PAMPs) and the debris of cellular damage (damage associated molecular patterns, DAMPs). They are found on many cells, including all myeloid and inflammatory cells, endothelial cells, glia, and, in inflammatory states, on neurons themselves. Ligation of the various TLRs trigger

specific downstream signaling cascades, which not only powerfully trigger the immune system, but also lead to autocrine, and in some cases autocatalytic, positive feedback amplification mechanisms to alert initially innate, and subsequently adaptive immune mechanisms. CD14 is the co-receptor for TLR4; MD2 is the soluble extracellular binding partner for TLR4 which actually binds endotoxin in a special groove within the extracellular, leucine-rich repeat zones of the arcs of TLR4. Heat shock proteins 70 and 90 also transduce signals at the cell membrane. Morphine and other opiates bind to this endotoxin binding groove on MD2-TLR4 with an affinity around 1,000 times less than that of endotoxin. Intracellular signaling from TLR4 is done via both myeloid differentiation factor 88 (MyD88) and toll-like/interleukin 1 receptor (TIR) adapting factor (TRAF)-dependent pathways. This signaling triggers the major mechanisms of phosphoinositol-3 kinase (PI3K) activation, mitogen activated kinase (MAPK), activating protein-1 (AP-1), nitric oxide synthase (NOS), transforming growth factor-β (TGFβ), the primary immune transcription factor nuclear factor-κB (NF-κB) and downstream cytokines, including TNFα, interleukin (IL)-1, IL-6, macrophage chemotactic protein-1/cytokine chemokine ligand 2 (MCP-1/CCL2), interferon regulatory factors (IRFs) 3 and 7, reactive oxygen (and nitrogen) species in part via mitochondrial uncoupling, many micro-RNA's (miR's) and acid sphingomyelinase.[22,41] These are all powerful effector mechanisms with known involvement in major inflammatory processes such as inflammatory cell adhesion, cell activation, vasodilation, cell growth and survival, apoptosis, fibrosis induction and scar formation, atherogenesis, carcinogenesis and metastasis. Elevated levels of the cytokines IL-1, IL-6, TNFα, and lymphocytes, monocytes, and C-reactive protein have been identified in opiate addiction.[42–46]

Understanding the primacy and power of TLR4 ligation introduces great elegance into a mechanistic understanding of the opiate dependency syndrome. In particular, whilst studies have been performed showing stimulation of the PI3K,[47] MAPK,[48] AP-1,[49] TGFβ[50] and nitric oxide synthase[51] systems by opiates, the concept that this can all occur downstream of TLR4 stimulation greatly simplifies conceptualization of its otherwise confusing clinical diversity. Clearly, the conception that these patients are chronically sub-clinically ill, and more particularly inflamed, explains many of the "sick cell syndromes" which accompany the inflammatory state, including immunostimulation, immunosuppression, and subtle and serious multiple endocrinopathies.

Cytokine cascades via inflammasome activation

Elevation of mature circulating IL-1 is pathophysiologically significant. As noted above, IL-1 is a proximal product of TLR activation. Indeed, the intracellular domain of the TLRs is known as the TIR, toll-like interleukin-1 receptor domain. However, transcription and translation of the IL-1 gene produces 34kD pro-interleukin-1 rather than its mature active 17-kD form. Proteolytic cleavage is required to release the active form. Within cells this cleavage is generally performed by caspase-1, which is a product of the inflammasome, a large multi-protein assembly. The cleavage can also be affected in the extracellular milieu by serum elastase or neutrophil-derived protease-3.[52] Inflammasome activation almost certainly occurs in COA although it has not been directly measured. It would be straightforward to do this simply by measuring key mediators released into the circulation. Inflammasome activation requires two signals to occur, the first an immune signal and the second a signal provided by diverse DAMPs and thought to be mediated through free radical release, potassium efflux, or extracellular ATP release, such as would occur with increased frequency around sick, damaged, or stressed cells.[53]

Cell–cell contact and microvascular egress

The role of the sphingomyelins is fascinating as signaling via the products of this pathway, such as sphingomyelin-1-phosphate (S1P) and its S1P receptors (S1PR), have recently been shown to control the binding of the endothelial cell–cell gap junction adhesion zones and the ability of inflammatory cells to egress the vascular system.[54,55] This is known to be a key step in generating both acute inflammatory foci and chronic inflammatory lesions such as are seen in atherosclerotic plaque formation. In the brain, the integrity of the blood brain barrier has been shown to be controlled by S1P-S1PR5.[56] This mechanism is harnessed therapeutically with the use of fingolimod

to treat the lesions of multiple sclerosis, a well-established chronic neuroinflammatory disorder.[57]

TLR/RLR co-immunostimulation induces immunosuppression

These data therefore imply that opiate-dependent patients are by virtue of this persistent TLR signaling chronically immune-stimulated[58] and because of a chronically dysfunctional immune system, immunocompromised.[59,41] For example chronic stimulation of TLRs by morphine has been shown to lead to down-regulation of TLR3 and TLR9[41] and uncoupling of NF-κB from cell surface signaling.[60] Moreover, since many immune pathways converge on NF-κB, stimulation of TLRs has been shown in some systems to interfere with Retinoic Acid-like Inducible genes (RIG)-like receptors (RLRs).[61] TLR3 activation has been shown to reduce the ability of cells to clear a mucocutaneous leishmania infection, which would otherwise be eradicated.[62] This clinical picture of immunosuppression[59] in the context of immunostimulation,[58] while at first appearing contradictory,[63] is also seen in the clinical disorders rheumatoid arthritis and systemic lupus erythematosus[64] and after immunosuppressive treatment with the calcineurin inhibitors cyclosporin A and sirolimus.[65] In this sense opiate-dependent patients are subject to a sub-acute, chronic endotoxaemia-like syndrome.[58]

Epigenetically driven immune processes

Epigenetic processes are also powerfully induced by TLR signaling, in particular TLR4 signaling. MicroRNAs (miRNA, miRs) are small 20 to 22 nucleotide long segments of RNA which target messenger RNA sequences (mRNA) in order to have them degraded by the argonaute spliceosome. Many miRs, particularly miRs-155, -146, -132, -21 and let -7i and -7e, are triggered by TLR activation due to the activity of RNA polymerase II, the main DNA transcription enzyme.[66] They generally have a role in shutting down and controlling the inflammatory cascades set in motion by TLR signaling. miR-155 transcription begins as early as 2 hours after TLR stimulation. As well as acting to reduce transcription of TLR4 molecules themselves, it similarly down-regulates many of the proteins in the TLR signaling cascade. FOXOP3 stimulates production of immunosuppressive T_{reg} cells and is suppressed by miR-155. miR-155 also suppresses the formation of T_H17 cells, which powerfully drive CNS inflammation in experimental allergic encephalitis and many other disorders. The principle immune transcription factor NF-κB1 is suppressed directly via miR-9, which also suppresses IKKα, one of the kinases immediately prior to P55/P65 NF-κB dimer proteolysis and nuclear translocation. TLR4 activation signals to NF-κB, which in turn induces miR-27b, which itself suppresses the anti-inflammatory transcription factor PPARγ. mi-132 suppresses p300, which is a transcriptional co-activator for cAMP response element binding protein (CRB),[66] which lies directly on the pathway of addictive drug transcriptional activation.[44] Powerful anti-inflammatory signaling via vagally-released acetylcholinesterase is suppressed by miR-132. miR-21 has been shown to reduce the tumor suppressor PDCD4 (protein-programmed cell death 4.[66] Hence, miRNA signaling links both inflammation and cancer, and shows how chronic immune-stimulation by TLR activation can lead to immunosuppression.

Immune oncogenesis

Signaling via TLRs and particularly TLR4 has been linked with 10 cancers.[67] It has also been linked powerfully with signaling via the forkhead transcription factors FOXO1a, which have long been known to be linked importantly with many longevity processes.[67,68] In addition, a linkage has been identified between macrophage TLR signaling and the induction of the metabolic syndrome and insulin resistance.[67,69,70]

Depending on the specific experimental protocol employed, the induction of endotoxaemia in experimental animal models is a condition which is frequently accompanied by a significant acute mortality. It is clear that acute mortality from endotoxic shock is not usually observed in our clinical patients; this is doubtless related to the lower binding affinity of morphine for the endotoxin receptor in comparison to its usual ligand. However, the very chronic nature of long-term opiate dependence suggests that in our clinical patients these changes will occur in the context of compounding interest over the very long-term. Furthermore, during the frequent daily withdrawal episodes experienced by our patients, it is likely that the dynamics of the binding at the receptor undergo drastic changes. These dynamics have not been studied in detail, but it is clearly a stressful state for the organism.

Since opiates have been shown to cause cellular apoptosis in some systems and to potentiate the apoptosis induced by other stressful factors (eg, tobacco) in others, it is likely that the pro-apoptotic effect of opiates compounds and exacerbates the pro-senescence, anti-cell growth effects.

Stem cell and regenerative implications of immunostimulation

The intracellular signaling from ligation of many immune-active receptors at the cell surface involves the Janus Activated Kinase (JAK)—Signal Transducer and Activator of Transcription (STAT) signaling cascade.[65] This system is well represented in stem cells, where in most cases it has a strong inhibitory action.[71] Indeed, of the four transcription factors known to be involved in the induction of embryonic stem cells, the gene promoter for nanog has a binding site for STAT transcription factors. From these data it is apparent not only that cell growth is subject to negative inputs from opiates directly, but that there is likely also a powerful interactive effect coming from opiate-induced immune activation and consequent stem cell suppression.[72]

In order to truly understand the pathophysiology of opiate dependence it is important to give careful consideration to factors such as those described. Autopsy series in developed countries where parenteral drug use is common frequently cite high levels of death due to overdose as the major risk factor associated with opiate use. Hence, in one large series with 3,803 deaths, 52% of 3,393 deaths due to a known cause were related to overdose and 37% were due to chronic disease.[73] However in another recent series reporting 705 deaths amongst a population in which drug use was almost exclusively by the oral or inhaled route, 83% of deaths were due to chronic disease.[74] This implies that a higher incidence of chronic disease may be underlying the morbidity and mortality profile seen in western countries. This may contribute towards explaining some of the overdose deaths which can occur somewhat mysteriously in association with normal or even low serum levels of xenobiotic intoxicants.

As naltrexone blocks opiate effects at classical opiate receptors and TLRs,[22] it can be expected to have a very different clinical toxicology profile to that of opiates. Indeed this whole class of agents of TLR antagonists is actively being developed by many drug companies for a wide variety of clinical applications. Newly developed agents include resatorvid, chaperonin 10, eritoran and various monoclonal antibodies.[75]

Metabolism and pharmacokinetic profile

As mentioned above naltrexone implants are typically composed of naltrexone, polylactide, and polyglycolide co-polymer, often with some triamcinolone to reduce local inflammation. Our attention shall therefore be directed to the naltrexone, followed then by the delivery system.

Naltrexone has been available since its synthesis in 1963. After oral administration, its serum concentration peaks at one hour, then declines with a half-life of around three hours. Naltrexone is metabolized in the liver to 6β-naltrexone, which is a less potent antagonist but has a longer half-life of 13 hours.

Data on the rate of decline of the serum level in naltrexone has been published for some of the implant devices, both for those active for one month[17] and for five months.[76–78] These data should be interpreted in light of the usual assumption that serum levels of 1 to 2 ng/mL are required to be clinically effective. It is both interesting and important that the very long terminal decay curve of NI is critical to protect the patients from late overdose even after the serum level falls below that required to control opiate use.[79]

Clinical Studies

Major studies of opiate related morbidity and mortality

Although the literature is replete with studies of opiate follow-up, many of these suffer from methodological shortcomings such as short follow-up periods or small patient numbers. To circumvent these issues, to confine the enormous subject within reasonable bounds, and to limit consideration to the most authoritative sources, it is proposed to focus on two large, recently published population-based studies. The first study of interest is a five year prospective study supported by the National Cancer Institute, was published in Lancet.[74] The second is a 21 year retrospective and historical review of the clinical experiences and mortality experience of Australia's most populous state, New South Wales. This second study appeared in Drug and Alcohol Dependence.[73] The first involved 8,487 opium addicted people and 41,558 controls (a total of 50,045 persons) and amassed 234,928 person-years. The second studied

42,676 opiate addicted patients over 21 years and analyzed 425,998 patient-years. The data of interest in the second study appeared as a Supplementary file in the Web Appendix 6. A subsequent publication which explored the cancer deaths in more detail in the Sydney experience has also appeared.[80] The two studies reported on populations who took opiates predominantly by the oral and inhaled routes, and by the oral and parenteral routes, respectively.

The prospective study from Iran was able to utilize advance statistical modelling to show that not only were opiates and death from many causes statistically associated, but the relationship was causal in the forward direction, from opiates to death. Cessation of opiate use required about 10 years for the effect of elevated mortality to regress to baseline.

The cause of death data from both studies is summarized in Table 2. The two studies report hazard ratios and standardized mortality ratios respectively. A number of striking findings stand out from this table.

Table 2. Effect sizes for death by organ system in opiate dependence.

Organ system	Khademi, 2012	Degenhardt, 2009, 2011
	H.R. (95% C.I.)	S.M.R. (95% C.I.)
Cardiovascular	1.81 (1.68–2.06)	2.2 (1.9–2.5)
Ischaemic heart disease	1.9 (1.57–2.29)	
Cerebrovascular	1.68 (1.29–2.18)	
Cancer	1.61 (11.28–2.03)	1.6 (1.4–1.9)
Oesophagus (females)	2.40 (1.13–5.10)	
Lung	2.27 (1.07–4.80)	3.6 (2.8–4.6)
Liver		6.9 (4.3–10.5)
Anogenital incl. cervix		2.8 (1.3–5.3)
Respiratory	3.78 (2.36–6.04)	3.9 (2.6–5.5)
Asthma	11.00 (3.97–30.50)	
COPD	5.44 (2.03–14.50)	
Digestive	3.12 (1.82–5.37)	7.7 (5.6–10.3)
Cirrhosis	2.28 (1.05–4.97)	12.5 (11.0–14.1)
External	0.86 (0.54–1.35)	9.6 (9.0–10.2)
Alcohol		5.4 (4.3–6.6)
Depression/ suicide		6.0 (5.5–6.6)
Overdose	25.4 (8.11–79.4)	43.5 (41.4–45.8)
Unknown	2.42 (1.59–3.57)	
All cause	1.90 (1.55–2.33)	
Males	1.63 (1.44–1.84)	5.9 (5.7–6.1)
Females	2.43 (2.05–2.88)	8.7 (8.1–9.2)

Degenhardt;[73,80] Khademi;[74] Data from Degenhardt 2009 is supplemented by that from Randall 2009.
Abbreviations: H.R., Hazard Ratios; S.M.R., Standardized Mortality Ratios.

Firstly, opiate use by either route is associated with greatly elevated mortality, even in the group using opiate by the inhaled and oral route. When adjusted for all other factors and when healthy patients are compared with opiate users this effect is 1.90 (95% C.I. 1.55–2.33). The effect appears to be compounded by use of the parenteral route. As noted above, 83% of deaths in the first study were related to chronic disease, as were 37% of those in the Australian study. Interestingly both studies reported higher HR/SMRs in females, by a factor of 1.49 and 1.47 respectively. This was highly statistically-significant (both $P < 0.001$). This finding remains unexplained. Conceivably, gender differences in immune function may be involved.

Secondly, opiates appear to be associated with cardiovascular death and cancer deaths, findings which, although they have been previously described, have not been demonstrated definitively and are not widely appreciated. Interestingly, similar comments apply to chronic digestive and pulmonary disease. Suicide, as a fatal end point of depression, can also be considered a neuroinflammatory disorder. The subsequent report from Sydney shows that rates of liver, lung and anogenital (including cervical) cancer were elevated and breast cancer rates were reduced.[80] Death related to alcoholic disease was noted to be elevated, which relates to earlier comments about disinhibition of the hypothalamic craving mechanism. The rates of overdose found in both studies is as shown. The Iranian study found that 3 of the 4 heroin users died during the five year study period. These deaths can probably be regarded as overdose deaths, and have been listed as such, but the assignment is tentative. The hazard ratio is also highly unstable in view of the small patient numbers.

Previous publications from Iran have found that in males, opium use is the strongest cardiovascular risk factor related to the need to open surgical coronary revascularization. Similarly in a carefully controlled Iranian study, opium use was found to be a more powerful predictive risk factor than tobacco use or diabetes[81] and to be associated with coronary artery disease occurring 4 years before that seen in a non-addicted population.[82,83]

Thirdly, the degree of agreement of many of the effect sizes calculated is remarkable. Hence there is

virtual identity for the effect sizes relating to cardiovascular disease, cancer, lung cancer, and chronic respiratory disease. Such near identity between two large and highly powered studies from two such divergent contexts provide powerful evidence for both the reality of the effect demonstrated1 and its magnitude.

Cardiovascular disease is now understood to have an inflammatory basis, as is much respiratory disease and hepatic cirrhosis. The inflammatory component of depression is widely known and widely studied. Moreover the contribution of chronic inflammation to many cancers is increasingly being appreciated.

Other studies show elevated rates of cardiovascular risk factors in opiate dependence, including tobacco use, weight gain, and unhealthy eating.[84–88] Various endocrinopathies have been reported in COA, including hyperglycaemia and diabetes, growth hormone stimulation, hypothalamic hypogonadotrophic hypogonadism, insulin resistance, hyperprolactinaemia, blunting of the hypothalamic-pituitary-adrenocortical responsiveness, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and osteopaenia-osteoporosis.[44,89–92]

It should also be noted that many of these changes are similar to those seen in biological human ageing. As so carefully demonstrated by the cardiovascular surgeons in Tehran, these changes occur several years earlier in opiate dependence.[82,83] Indeed, in these studies opium use in men was a more powerful predictive factor than diabetes.[81] Similar observations have been made for other age related indices such as hair greying, chronic periodontitis, and stem cell depression.[72,93–95] Cancers of the esophagus, larynx, and bladder have also been reported at elevated rates in large Iranian studies.[96–98]

Since naltrexone has been shown to reverse the proinflammatory effects of TLR ligation, it is expected that any of these pathologies will reverse under long-term antagonist treatment.

Oral use of opioids

An important question relates to whether these considerations are different for opiates used for clinical purposes such as long-term pain relief. The management of long-term pain is a difficult and very real clinical problem, and one upon which much research has been focused in recent years. It should however be noted that the above pathophysiological discussion is not specific to opioids administered by any particular route. Hence large studies have found that mortality amongst patients given opiates for pain is also greatly elevated, and although these publications did not provide detailed cause of death data, it may reasonably be surmised that pathophysiological mechanisms such as those described above contributed to the elevated rates of mortality observed.[99,100] Moreover the large Iranian study discussed above considered patients in whom opiate use was via the oral route.[74] The point was also made in that study that the level of use of these patients was relatively low. The large Australian study described in detail above also considered the standardized mortality rate (SMR) of patients in treatment and patients out of treatment, which may be considered as patients using mainly oral narcotics and patients mainly using parenteral routes of administration.[73] The SMRs from all causes were greatly elevated in both groups, though more so in the group using parenterally. Hence it is likely that pain patients exposed to long-term clinical use of opiates also experience similar risks, although somewhat less so than those exposed by parenteral routes. This explains some of the present research drive to develop newer non-addictive forms of analgesics which are not immune-active.

Randomized clinical studies of extended release naltrexone

Although there are several anecdotal case reports and clinical series relating to extended release naltrexone (EX-NTX), for the sake of conciseness and quality of evidence, the author's intention is to confine the present discussion to the randomized clinical trials of EX-NTX.

Table 3 shows a summary of six recently published trials of EX-NTX.[2,17,19–21,101] Together this represents 384 patients treated in the active implant arms and 321 in the control groups. The studies are not all the same and their differences in design together provide a useful overview of a diverse clinical experience with EX-NTX. Some of the statistics listed in the table have been quoted from the publication concerned and some have been recalculated using EpiInfo software (Version 7.0.8.3, CDC, Georgia) or "R" (Version 2.13.1, CRAN Archive), based on the published data. Preliminary interim analysis and results from a large

Table 3. Summary of randomized clinical trials.

Study	Implant type	Sample size	Median duration	Abstinent	*P*	Opiate dependence	*P*
		Ntx inj./ctl	Heroin dependence				
Comer[17]	Depotrex IMI	42/18	12.5	13.2–60.1	<0.001		
Kunoe[21]	Go medical	29/27	7	3.85 (1.08–13.75) (T.C.)	0.035 (T.C.)	0.225 (0.07–0.69) (ITT)	0.015
Hulse[20]	Go medical	35/34*	8.4	4.70 (1.68–13.10)	0.0036	0.12 (0.04–0.39)	<0.001
Kruptisky, 2011	Vivitrol IMI	126/124	10	1.58 (1.06–2.36)	0.0002	0.0504 (0.0066–0.3846)	<0.0001
Tiihonen[2,§]	Prodetoxone	50/50	8.9	2.6 (1.40–4.80)	0.0008		
Krupitsky[101,**]	Prodetoxone	102/102/102	8.0	9.31 (4.45–19.44)	$<10^{-16}$	0.29 (0.25–0.35)[#]	$P < 0.001$

Study	Craving	Quality of life	Deaths	Reactions
			Ntx v ctl	
Comer[17]	$P < 0.001$	N.S.	0 v 0	Minimal AE's, usually mild; injection site reactions—moderate
Kunoe[21]	–38.5 ($P < 0.01$)	+6.0 (1.2–10.7)	1 v 1 (ITT); 0 v 2 (T.C.)	3 local reactions, 3 systemic allergies
Hulse[20]			0 v 0	Withdrawal; moderate local reactions
Kruptisky, 2011	–10.8 ($P < 0.0001$)	+5.09 (2.09–8.09)	0 v 0	No suicides, no SAE's, all mild-moderate/unrelated to study drug
Tiihonen[2,§]	Reduced equally in both groups	+8.1 ($P = 0.004$)	0 v 0	Mild-moderate
Krupitsky[101]	Reduced by treatment	Less HIV risk behaviour	0 v 0 v 0	Mild-moderate—wound infections and local reactions—easily managed

Notes: *This trial compared implant to oral naltrexone; **this trial compared naltrexone implants, oral naltrexone and placebos; [§]this trial studied patients dually addicted to heroin and amphetamines; [#]reports the number of Opiate positive Urine Drug Analyses.
Abbreviations: Ctl, Control; Ntx, Naltrexone; Ntx Inj., Naltrexone Injection; ITT, Intention to Treat analysis; T.C., Treatment Completion analysis.

Russian study have long been available.[12] However, these have recently been superseded by the definitive report from the completed study,[101] and it is these latter results which are included in the present review.

It is particularly noteworthy that whilst most of these studies are not numerically large, they uniformly report highly statistically-significant results. That so uniform a pattern of results has been reported from so many locations is strongly indicative of a powerful and reliable treatment effect. Indeed the Krupitsky 2011 paper included patients from 13 sites in Russia. The question of EX-NTX is particularly relevant to the Russian Federation as agonist treatment is not lawful in that country, as indeed it is not in 122 of the 192 (63%) member nations of the United Nations.[2,12,19]

Most studies have compared naltrexone to placebo. The Comer study compared 18 placebo-treated patients to 22 patients treated with two Depotrex injections and 20 patients treated with one. The serum levels achieved in the single injection group were quite low, with mean peaks of around 2 ng/mL, so that this groups represents a worst case scenario. Hulse compared depot naltrexone with oral naltrexone. Tiihonen studied a group of dually addicted heroin and amphetamine-dependent patients to more closely approximate the real world experience in contemporary Russia. Krupitsky notes in many reports that most of the cohorts upon which he reports are young, with a mean age of 22, and only 2.5 years of drug use.[12] Most live at home with their parents. Otherwise the duration of heroin dependence seen in the trial patients listed is typical of that seen in many series in the literature. Both the Krupitsky 2010 and 2012 studies utilized 3 two month Prodetoxone implants.[12] Similarly the Krupitsky 2011 study utilized 6 once-monthly injections of Vivitrol.[19] This is an important design nuance as much of the discussion and controversy relating to NI overlooks the fact that, as in agonist treatments, repeated administrations of the treatment can be performed. NI is not necessarily a "one-off" treatment as it is frequently describe. Indeed, it is important to note that in many of the centers where it is used most successfully, repeated administration, along with psychosocial support, are commonplace.[102] Finally, in the most recently published study, Krupitsky compared three groups, with 102 participants in each of the implant naltrexone, oral naltrexone, and placebo (implant and oral) groups.

As the indices reported in the different studies varied, it is not necessarily a simple exercise to compare their results. All of the studies found a highly statistically-significant increase in the achievement of opiate-free urine results with odds ratios ranging from 1.58 to 4.7 and above. As listed, the *P*-values are highly significant. The Comer study was important as it showed a dose-dependent response with the two injections performing better than one on most measured indices. The Comer report also calculated a number needed to treat (NNT) index. This figure was 2.8 on an intention-to-treat basis and 2.36 on a treatment-completion basis.[17] These figures are very low indeed and indicate a much higher treatment effect than many other commonly used treatments such as anti-hypertensives, antibiotics in primary care, and lipid lowering agents.

Conversely the rate of return to dependent drug use was shown to be statistically significantly reduced, with odds ratios from 0.05 to 0.22.

Five of the studies reported marked reductions in opiate craving scores. Interestingly the Comer study, which was numerically small, also reported highly significant reductions in craving for cocaine, benzodiazepines, amphetamine, and methadone (all $P < 0.05$). The reduction in cannabis craving in that study was $P = 0.08$, which did not quite reach significance. However, cannabis was smoked by a minority of study participants, which may not be representative of other opiate-dependent populations.

Interestingly most studies reported significantly reduced rates of depression or enhanced scores for general well-being.

The largest study in this area which has just been published is that by Krupitsky in 2012.[101] It is noteworthy for several reasons. Whilst agonist medications are not considered legal in the Russian Federation, the nation seems particularly well covered by a network of 138 addiction dispensaries, including 115 inpatient detoxification units and 12 addiction hospitals with over 25,000 beds and 5,600 psychiatrists and narcologists working mainly in addiction. The authors compared the relapse free outcomes in three groups (n = 102 each) of implant naltrexone, oral naltrexone, and placebo groups with blinding by placebos for both implants and tablets. All patients required accountability to a suitable caretaker such as a parent or partner—as is typical of Russian studies—and

the unavailability of a caretaker was sufficient reason for exclusion from the study (13 patients). The mean age was 28.2, rather older than many of the other studies. The mean duration of heroin use was 8.0 years. The protocol involved the use of three implants at bimonthly intervals. However, patients who relapsed back to heroin use were excluded from further participation in the study. Since in the real world patients would simply be re-implanted, the results of this study should be considered as the lower bound of the efficacy of NI. These authors reported that 54 of 102 NI patients (52.9%) were relapse-free at six months, which was significantly better than the outcome in the double placebo group (log rank statistic = 68.4, df = 1, $P = 6.17 \times 10^{-17}$). Patients also received follow-up nine and twelve months after trial registration, but results at these time points were poor. The authors concluded that extended periods in treatment were required for most patients. Oral naltrexone performed better than the double placebo group on both clinical relapse and opiate positive urine criteria ($P = 0.014$ and 3.4×10^{-6}). No deaths were reported.

Meta-analysis of results

Patients in these studies can largely be considered similar. Perhaps the largest differences related to study duration, which were of 2, 6, 6, 6, 2.5 and 6 months. Other individual features of the studies are shown in Tables 3 and 4. Patient exclusion criteria in all studies were similar. Differences in design have been noted above. For the reasons stated above, these experimental protocols likely represent the lower limit of the effectiveness of EX-NTX.

The results from the four studies reporting six month results may be pooled directly. Together these four studies document the course of 292 EX-NTX patients, 136 oral naltrexone patients, and 253 placebo-treated patients. The numbers reported to be drug-free (either as clinical abstinence or opiate-free urines) were 132, 25, and 44 respectively, representing abstinence rates of 45.2%, 18.4% and 17.4% (Table 4). When the four chi-squared tables implies in Table 4 are considered serially they are significant with an adjusted odds ratio of 6.00, (95% C.I. 3.87–9.50, $P < 10^{-10}$).

Adverse events in trials

The study by Kunoe was the only one to document a death in the program. In that study one patient died in the placebo group. One patient assigned to the NI group left hospital on day three before he could commence NI. Therefore, he was allocated to the NI group in the intention-to-treat analysis (ITT) and to the placebo group on a treatment completion (TC) basis. Also pertinent to this question is the report of a follow-up study conducted after a large Russian trial of 306 patients. Whilst no deaths were reported in the NI group, there was one in the oral naltrexone group and four in the placebo group.[103]

Interestingly it has been reported that of 45,000 patients treated with NI in the USA, only 19 deaths in such patients have been reported to the FDA. Only one of these has been ascribed to possibly being associated with the NI.[103]

Adverse effects were generally reported as mild to moderate. Most involved the injection site and were readily manageable, although on occasion the implant was removed due to infection.

Three study reports[2,17,19,101] mentioned that liver enzyme elevations were not clinically problematic at the usual doses employed. This contrasts with the FDA black box warning, relating to a potential elevation of serum liver enzymes, which appears on the product information for oral naltrexone, and which was derived from studies of the use of the drug at

Table 4. Meta-analysis of 6 month EX-NTX studies.

Study	Implant type	Duration	Sample size			Abstinent		
			Ntx inj.	Oral	Placebo	Ntx inj.	Oral	Placebo
Kunoe[21]	Go medical	6 months	29		27	11		5
Hulse[20]	Go medical	6 months	35	34		22	9	
Kruptisky, 2011	Vivitrol IMI	6 months	126		124	45		28
Krupitsky[101]	Prodetoxone	6 months	102	102	102	54	16	11
Totals			292	136	253	132	25	44
% abstinent						45.21%	18.38%	17.39%

high dose. Four reports specifically stated that there was no cases of implant removal by patients.

Two other theoretical risks were also discussed by some authors but not observed in practice. These were the risk of opiate overdose by overriding the competitive antagonism of the antagonist-induced blockade and the risk of late overdose after the implant had worn off.

Safety

Naltrexone's side effects are well established. Indigestion, insomnia, and depression are commonly reported in opiate-dependent patients, but these generally relate to residual detoxification symptoms.[104] They are readily managed in the clinic. In patients who are truly drug-free, naltrexone can be administered almost without apparent effect. Indeed, it is so benign that it has been referred to as a "non-drug" by leading researchers from NIDA.[9]

Of more concern has been the hypothetical overdose risk, which in the case of naltrexone may relate to the dual scenarios of patients either attempting to override the competitive blockade effect whilst the implant is still active, or alternatively a return to their use after the period in which the implant is active. The first scenario has not been reported clinically. As noted below, the second case is only seen very rarely.

Tissue reactivity has been a major concern with implantable NTX or EX-NTX. Recent studies of the Australian implant, both in rat and in human trials, have not found severe local reactions. In 58 biopsies taken from clinical samples from 1 to 38 months, a moderate level of fat necrosis was seen in the first 6 months, falling to a mild level over the next 12 months. Some of this was ascribed to the local response to surgery. No foreign body reaction, fibrosis, or chronic inflammation was detected. In most cases no implant material was detectable at 25 months or later.[105] Similar largely benign results were obtained in rats.[106]

A similar ultrasound study performed in 71 patients with the Perth NI in situ on days 2 to 1808 after implantation showed that the while implant beads were originally dispersed throughout the subcutaneous tissue, they gradually coalesced into a single lump as biodegradation ensued. No local naltrexone material was detectable by day 1201. These changes correlated with clinical findings on palpation.[107]

Mortality studies

The suggestion that NI may be associated with inordinate death rates, as has come from certain uncontrolled case series[108,109] has generated significant controversy and has formally been refuted by many authorities.[103,110–117] As noted above, elevated death rates have not been a feature of any of the randomized trials of NI, nor has it been problematic either in 45,000 US patients treated, nor in the follow-up period after completion of some of the large Russian clinical trials.[103]

Moreover the issue has been carefully addressed in at least two clinical reviews of large case series. One study from Perth compared the survival experience of 341 NI treated patients with 553 methadone registrants treated between 2001 and 2002 and observed for 1,594 and 2,572 patient-years. They found 6 deaths in the NI group, a crude mortality of 1.8%, and an age standardized mortality compared to methadone of 0.645 (0.123–1.17). In four cases where the cause of death was known, death occurred by motor vehicle trauma in two cases—one of which was suicide—while the other two deaths were caused by a fit and an accidental polydrug overdose. This last death occurred 1026 days after the last NI was administered. One further patient was treated with both methadone and NI, dying 277 days after methadone and 899 days after NI, from a combined polydrug overdose. Deaths in the methadone group largely reflected overdose mortality, as is generally seen.[118]

This group has also done careful follow-up work with a cluster of especially chaotic patients whose clinical course was marked by repeated overdoses, and who, in the normal course of events, might have been expected to experience an inordinate elevation of their mortality.[119] They found that prior to NI antagonist treatment, 7 patients had 82 events requiring hospital admission over 34.4 patient years of observation. However, after NI treatment 8 patients experienced 21 events in 98.5 patient-years of observation, whereas 234.4 would have been expected at the prior rate. This represents a standardized mortality rate of 0.0009 compared to their pre-treatment mortality. The two time periods measured were 1,794 and 4,494 patient days respectively. The two event rates were 0.0457 per patient-day (99% C.I. 0.0345–0.0603) and 0.0047 (99% C.I. 0.0015–0.0111) which are very clearly non-overlapping (Fisher test: O.R. = 0.1023; 95% C.I. 0.0599–0.1674, $P < 10^{-15}$).

This work was subsequently expanded to show a reduction from 21 overdose episodes in 20 clients in the six months prior, to zero overdoses in the six months after NI treatment.[120]

A second study also from Australia followed 255 NI and 2,518 buprenorphine treated patients for 1,332 and 8,030 patient-years.[121] The crude mortality observed in each group was 3.00 and 5.35 per 1000 patient-years, and the age standardized mortality rate of NI compared to buprenorphine was 0.676 (95% C.I. 0.014–1.338). Most age and sex stratified subgroup comparisons within this study favored the NI group ($P = 0.002$). Death in the NI group occurred 324 to 2,209 days after implant insertion. Identified causes of death in these NI patients included suicide, murder, polydrug overdose (at 324 days), and cerebral abscesses and status epilepticus from intravenous injection of buprenorphine. In particular the in-treatment mortality for NI patients, where treatment was defined as the period for which the implant was working, was 0.00 in 258 patient-years.

Together these two studies present reassuring registry-controlled data from 596 patients and 2,927 patient-years of observation.

Combined with other remarks, such as the comment that only one report of death in 45,000 patient treatment episodes reported to the FDA was believed to possibly be implant-related and the fact that there appear so far to be no mortality in the 305 treated Russian patients post-trial,[103] the overall picture of mortality emerging from the literature after NI is reassuring.

Patient acceptance

Whilst it is widely said that naltrexone may have poor clinical uptake because it does not have the euphoric effects of agonist treatments, in practice there does seem to be keen demand in many countries for such treatments. The congruence between the often stated wish of drug-dependent patients for the drug-free lifestyle and the non-addictive nature of antagonist based treatments has been noted above.[6] It is difficult to argue that patients should not at least be given the option to choose which treatment pathway they wish to pursue. In this context, the right to choose multiple treatment episodes and different treatment modalities at different phases of their addictive history appears to be difficult to refute.

Place in therapy

The array of treatments provided to opiate-dependent patients at the present time appears to be related to the confluent factors of the historical availability, development of agonist treatments, and the early failure of implantable forms of antagonists apparently related to difficulties of local tissue reactivity. However, the present range of treatment options was the result neither of rational clinical trial design nor of an adequate understanding of the fundamental nature of the deranged pathophysiology of opiate addiction. At the time of writing, opiate addiction is still not completely understood either in its neurobiological or its immunostimulatory-immunosuppressive dimensions, and the definitive series of clinical trials comparing current agonist based and NI treatments is yet to be conducted.

Data presented in this review shows that issues of efficacy, safety, and patient uptake have been addressed beyond reasonable dispute. Naltrexone implants and depot injectables are available from several countries. As the treatment becomes more widespread, and as regulatory authorities permit their increasing use because of this gathering data, it seems that a more rational, evidence driven approach to treatment selection will become possible.

Whether psychological testing or pharmacogenomic approaches will allow the prediction of optimum treatment routes based upon personal genomic or epigenomic profiling is a subject for further research.

Conclusions

At the time of writing there appears to be an increasing and overwhelming preponderance of evidence relating to the risks posed by indefinite opiate agonist treatments on the one hand, and the safety, efficacy, and patient acceptability of NI on the other. Randomized clinical trials have now demonstrated an increase in the drug-free rate of 1.6–4.7 fold and more in trials controlled by urine drug screen data. Earlier fears in relation to local tissue reactivity appear to have been addressed by modern delivery techniques. A small case series raising concerns in relation to possible implant associated mortality has been allayed by large series. These large series together report data on registry follow-up of over 900 patients in Russia and Australia and over 3,000 patient-years, and can be analyzed together with

the US FDA post-marketing campaign feedback data on the 45,000 patients in whom Vivitrol EX-NTX has been used. Indeed, in Western Australia, NI is used interventionally in a highly effective manner to abort highly lethal, repeated overdose behavior in especially chaotic and unstable opiate dependency.[119,120] NI was used in such a manner as to completely bypass the earlier, greatly elevated mortality associated with agonist stabilization.[73]

With the registration of EX-NTX for opiate dependency by the FDA and major studies coming from the Russian Federation, where agonist treatments are not allowed, it appears that important studies directly comparing NI and agonist treatments may soon be undertaken. Critically important and as a background and basis to this important work in addiction medicine is an improved understanding of the toxicopathology of long term opiate dependence, which is itself emerging as an important example of chronic inflammation and pro-senescence activities and the myriad benign and malignant clinical syndromes which can result from such pathophysiology. It is to be hoped that long term studies adequately powered to address subtle sub-clinical age and immune-related pathologies will be part of the new generation of trial designs. For NI and EX-NTX the future looks promising and exciting. As our understanding of the basic biology underpinning this work improves, it is likely that the benefits will also spill over to the population at large due to the understanding and management of degenerative age-related disorders which we see in our drug-dependent patients years before they are seen in the rest of the community. These disorders include atherosclerosis, dementia and neuropsychiatric syndromes, osteoporosis, cancer, and perhaps even the aging process itself.

Author Contributions

Conceived and designed the experiments: ASR. Analysed the data: ASR. Wrote the first draft of the manuscript: ASR. Contributed to the writing of the manuscript: ASR. Agree with manuscript results and conclusions: ASR. Jointly developed the structure and arguments for the paper: ASR. Made critical revisions and approved final version: ASR. All authors reviewed and approved of the final manuscript.

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