

Naltrexone for Probationers and Parolees

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Abstract

Heroin addiction is a chronic disorder usually associated with crimes to obtain funds for the purchase of this illegal drug. When these individuals are apprehended and incarcerated, they temporarily obtain drug free status, but relapse quickly upon release. There is an FDA approved medication, naltrexone, that could prevent relapse and thus break this revolving door cycle. In combination with counseling, former inmates could devote energies to legal jobs or job training instead of drug-seeking. Major reasons for non-usage of this medication appears to be lack of knowledge about the medication and fears that the use of a medication that blocks opiate receptors might somehow be unethical.

This special issue presents data, discussion and suggestions regarding the ethical use of naltrexone in incarcerated populations or those under supervision of parole or probation.

Naltrexone was developed by the National Institute on Drug Abuse in the 1970s and early 1980s (O'Brien, Greenstein, Mintz, 1975). It was approved by the FDA for the treatment of heroin addiction in 1984 (Greenstein, Arndt, McLellan & O'Brien, 1984) and in 1995 it was also approved by the FDA in the treatment of alcoholism (Volpicelli, Alterman, Hayashida & O'Brien, 1992). It was one of the first "orphan drugs" developed primarily from federal research dollars, since there had been very little interest in the problems of alcohol or opiate dependence by pharmaceutical companies. (Institute of Medicine, 1995). A new, extended release formulation of naltrexone has been developed and was approved by the FDA in 2006 for use in the treatment of alcohol dependence. (Garbutt, Kranzler, O'Malley, Gastfriend, Pettinati, Silverman, Loewy & Ehrich 2005) This same slow release technology has been used for other medications such as anti-psychotics and growth hormone. The extended release formulation requires an injection in the deep muscle of the gluteus maximus, but then provides gradual release of the naltrexone at a steady state for 30 days, providing long-acting protection from alcohol (or opiate) effects. (Garbutt, Kranzler, O'Malley, Gastfriend, Pettinati, Silverman, Loewy & Ehrich 2005) Since alcohol and opiate addiction are associated with significant crime problems in this country; and since many of those now in prisons or on probation/parole have underlying opiate or alcohol problems; and since the criminal justice system is the major source of addiction treatment referral in this country - the availability of naltrexone, especially in an extended release formulation may be seen as offering new options to the management of addiction related crime through the treatment of opiate and alcohol addiction. But -- is it legal, ethical or practical to offer naltrexone in lieu of incarceration -- or as a conditional part of probation/parole? Can a patient be given

a truly informed choice about accepting naltrexone when the other option may be incarceration? Can a patient be forced to accept naltrexone even if they do not want it?

These important and real-world questions regarding the use of naltrexone form the basis for the present special issue of the Journal of Substance Abuse Treatment. In turn, this article introduces naltrexone, the results of treatment studies with this medication, and introduces the ethical and legal issues surrounding its use in criminal justice settings. Subsequent papers within this issue offer specific background and guidelines to its ethical, practical and legal use.

Opiates, Opioids and the Receptor System

The development of naltrexone is the result of neuroscience research that identified specific receptors for opiate drugs that are present in a wide variety of organ systems throughout the body. These receptors are very similar across species, even lower species, indicating that they have been present since early in evolution. Subsequently, peptide neurotransmitters and hormones that act on these receptors were discovered and the whole system is now called the endogenous opioid system. Drugs such as heroin made from the opium poppy fit very well into these receptors and thus they can turn them on just as well or in some cases even more effectively than the natural hormones. (Terenius, 1996) Opioids are drugs that are synthesized in a laboratory and thus are not direct opium derivatives. These synthetic opioids possess structural similarities that cause them to also act on opiate receptors. The natural peptides synthesized in the body that act on these receptors are called endogenous opioids. The opiates and opioids continue to have very important medicinal uses, but they can be

abused. The principal opiate of abuse is heroin which has been a problem in the U.S. since the early 20th century and since the 1990s, cheaper and more potent heroin has worsened the epidemic.(Caulkins, 2001)

The Science Behind Naltrexone

Opiate drugs are called *agonists* because they fully activate opiate receptors. Drugs such as heroin, morphine, methadone, oxycodone and codeine are all agonists, because they all activate one or more of the opiate receptors, particularly the “mu receptor” which is believed to be the most important receptor in producing pain relief. In contrast to these well known opiate agonists, naltrexone is considered to be an *antagonist* at these receptors. It was first studied in human subjects in 1973.(Martin, Jasinski & Mansky, 1973)

This antagonist medication can occupy the opiate receptors but not activate them. Indeed occupation of opiate receptors by an antagonist such as naltrexone, *prevents* other opiates or opioids from being able to activate opiate receptors. (O'Brien, Greenstein, Mintz, & Woody, 1975) If naltrexone or its short acting antagonist cousin, naloxone is given to a person who is already taking opiates whether they are dependent or not, the antagonist will displace the agonist from the receptor and produce symptoms of opiate withdrawal. (O'Brien, Testa, O'Brien, Brady & Wells, 1977) If naltrexone is given to someone who is not taking opiate drugs, it will displace any endogenous opioids that are adhering to the receptor and block any additional opioids from attaching to the receptor. This blockade has been utilized as therapy because it prevents the effects of any opiate such as heroin.

Another benefit of naltrexone, discovered at the University of Pennsylvania and the Philadelphia VA Medical Center in the late 1980s is its therapeutic effect for alcoholism. (Volpicelli, Alterman, Hayashida & O'Brien, 1992) It was found that some alcoholics, particularly those with a family history of alcoholism, have endogenous opioid systems sensitive to the ingestion of alcohol.(King, Volpicelli, Frazer & O'Brien, 1997) In these drinkers, endorphins are released by alcohol and this produces euphoria. In turn, treatment with naltrexone can block this euphoria and aid in the prevention of relapse.

Clinical Properties of Naltrexone

Naltrexone produces no opiate-like effects. Normal volunteers given naltrexone will sometimes report vague, unpleasant feelings thought to be caused by blockade of normal endogenous opioids (endorphins).(Hollister, Johnson, Boukhabza,1981) Nausea or vomiting can occur in patients who are actively using opiates because naltrexone will precipitate withdrawal symptoms as described above. Side effects were few in the large study of alcoholism mainly a small increase in nausea compared to the placebo group.(Garbutt, Kranzler, O'Malley, Gastfriend, Pettinati, Silverman, Loewy & Ehrich 2005) Liver toxicity has been a potential concern because when naltrexone was given in doses 7 times the normal level in an attempt to treat obesity, liver enzymes became elevated. They returned to normal when the medication was stopped. In studies of alcoholics and heroin addicts, liver toxicity has not been noted although liver enzymes have been carefully studied.(Croop, Faulkner & Labroila, 1997)

There are therapeutic benefits derived from the blockade of opiate receptors in formerly dependent addicts because injected opiates such as heroin are denied access to the receptors and thus do not produce euphoria. Relapse to opiate addiction is therefore impossible. Most heroin addicts, however, have no interest in taking a medication that does not make them feel good. In contrast, methadone and buprenorphine act at the same receptors as heroin and produce feelings of comfort if not high. Thus heroin addicts who have the choice of treatment with an antagonist such as naltrexone or an agonist such as methadone or buprenorphine will almost invariably choose the agonist. White collar addicts such as physicians, nurses, pharmacists and others who do not wish to be on methadone are often motivated to be treated by the antagonist strategy. Naltrexone has been the treatment of choice for physicians with opiate addiction problems since the 1980s.(O'Brien, Woody & McLellan, 1986)

Of course naltrexone only blocks opiates. There is no apparent effect on reducing cocaine use. On the other hand, there is little evidence that patients who stop use of opiates spontaneously initiate non-opiate drug abuse.(Cornish, Metzger, Woody, Wilson, McLellan, Wandergrift & O'Brien, 1997) For example, unless a patient had prior problems with cocaine abuse, few take it up *de novo* when treated with naltrexone. Naltrexone also does not affect other categories of drugs such as benzodiazepines or amphetamines. (Cornish, Metzger, Woody, Wilson, McLellan, Wandergrift & O'Brien, 1997)

A logical question when naltrexone is considered is what are the negative effects of blocking the body's endogenous opioids? Doesn't this system have some normalizing function that would be impaired by interfering with it? The answer is that we don't fully

understand the normal physiology of the endogenous opioid system. We know that it is involved in the internal blocking of pain perception. This is believed to have developed as part of the "fight or flight" system so that in an emergency situation, the organism isn't impeded by the perception of pain. Endorphins are also involved in the regulation of mood and appetite. There must be redundant systems for this because most patients suffer no perceptible effects from long term blockage of these receptors.

While we do not yet have full knowledge about the long term blockade of the endogenous opiate system we do know the practical effects from using antagonist medications over long periods of time. There is a clear literature describing the effects of treating patients (many of them physicians) for 15-20 years by continuous opiate receptor blockade with naltrexone and there were no apparent side effects. (O'Brien, Woody, McLellan, 1986; Ling & Wesson, 1984) This treatment is particularly useful for anesthesiologists who must administer opiates to their patients on a daily basis. Knowing that their receptors are blocked removes the temptation to divert opiates for their personal use.

Naltrexone for prevention of relapse in parolees

Heroin addicted individuals commit many crimes to support their habit. (Ball, 1991) Usually these are non violent crimes, but when arrested and convicted, there may be a period of incarceration. The criminal addict becomes abstinent after going through withdrawal in custody, sometimes without the aid of medication. Despite not using opiates for a long period, incarcerated opiate addicts relapse to heroin or other drugs at an alarming rate following their release from custody, even when they are under supervision

by a parole officer. (Cornish, Metzger, Woody, Wilson, McLellan, Vandergrift & O'Brien, 1997; Dolan, Shearer, White, Zhou, Kaldor & Wodak, 2005; Hser, Hoffman, Grella & Anglin, 2001) It may be thought that the period of incarceration would "get the opiates out of their system" and "teach them a lesson" but this is apparently not enough to prevent re-addiction and re-incarceration in a majority of those opiate addicted prisoners (Dolan, Shearer, White, Zhou, Kaldor & Wodak, 2005; Hser, Hoffman, Grella & Anglin, 2001) This is where the availability of naltrexone may provide real benefits to the parolee, the criminal justice system and the public at large. Uncontrolled trials suggested that use of naltrexone could be helpful. (Capone, Brahen, Condren, Kordal, Melchionda & Peterson, 1986) In the only randomized, controlled clinical trial of probationers with a history of opiate addiction, Cornish et al (Cornish, Metzger, Woody, Wilson, McLellan, Vandergrift & O'Brien, 1997) found that 59% of opiate addicted parolees who received standard parole supervision – but not naltrexone – relapsed and were re-incarcerated within a year following their release. In contrast, a randomly assigned group of similar parolees who also received standard parole supervision but also naltrexone from a research nurse stationed at the parole office had a relapse rate of only 25%.

In this regard it is important to emphasize that naltrexone treatment is not an experimental intervention. It does not require an informed consent procedure any more than does the use of any other FDA approved medication. It is not addicting, has few side effects and is not considered to be a dangerous drug. It does have a "black box" warning in the PDR about the potential for liver damage as described above(O'Brien & McLellan, 1996), but this was a compromise of the approval process.

Adherence and the New Naltrexone Formulations

One of the problems that has been associated with naltrexone is the compliance or adherence rate. Like any other medication (O'Brien & McLellan, 1996) patients forget or resist taking naltrexone – thus limiting its potential effectiveness. Beyond these general factors, which are common to most medications and patient populations, there are special circumstances limiting the daily taking of naltrexone. First, many opiate addicted patients have disorganized lives and this disorganization leads to forgetting. Second, it is a fact that naltrexone prevents the ability to use heroin or other opiates – something that the individual may not wish to give up, consciously or unconsciously. Finally, there are no reinforcing pharmacological effects from taking naltrexone as one gets from taking methadone or buprenorphine – it doesn't make the patient feel good.

Because of these problems with adherence to daily medication schedules, various companies have been working to develop depot or sustained released versions of naltrexone to reduce adherence problems. For example, the Alkermes company has just received approval for what has been called a "sustained release" formulation delivered via injection in the deep muscle of the gluteus region. (Garbutt, Kranzler, O'Malley, Gastfriend, Pettinati, Silverman, Loewy & Ehrich, 2005) The naltrexone is suspended in a composite solution of essentially the same substance used to make surgical sutures. As the material dissolves over a 30 day period, the naltrexone is released, providing continuous, steady-state medication throughout the time period. The other two versions use a similar technology. Whether called depot or sustained release, the product provides continuous, steady-state medication for 30 to 40 days. In Australia, a group of

physicians not connected with a pharmaceutical company has been testing a larger version that is surgically implanted under the skin and is expected to last for six months.

Is Naltrexone an Ethical Part of Treatment for Criminal Justice Clients?

The judicial system has responsibility for convicted criminals and their rehabilitation should be a goal, not simply punishment. Those with a history of heroin addiction will almost always relapse when they are released from incarceration (Dolan, Shearer, White, Zhou, Kaldor & Wodak, 2005; Hser, Hoffman, Grella & Anglin, 2001). Group therapy and counseling in prison have little effect on long term outcome. Even after rehabilitation in a therapeutic community, relapse is frequent. Relapse prevention treatment in the home environment is essential – both for the direct benefit of the recovering offender, but as importantly, for the protection of society at large. Drug free treatment of heroin addiction has had minimal success despite decades of effort. (Keen, Oliver, Rowse & Mathers, 2001) Methadone or buprenorphine would be very effective in preventing relapse, but most judges and probation officers are philosophically opposed to this approach as being too similar to heroin itself.

Because of the problems faced by opiate addicted patients in remembering to take daily medications, we believe sustained release versions of naltrexone are likely to be very successful. If a naltrexone-protected patient tries to get high, they will feel little or no effect from that injection. This may lead to some frustration, but also in many cases, a liberating feeling. For the first time, they are able to move about their neighborhoods with no risk of relapse to heroin. Some report this as a life changing experience. But is it

ethical or legal to demand that an offender with an opiate problem receive naltrexone – particularly a long acting naltrexone preparation - as part of their parole or probation?

It is again important to point out that naltrexone treatment is not an experimental intervention. It does not require an informed consent procedure any more than does the use of any other FDA approved medication. Doctors with opiate addiction have been offered naltrexone as part of a mandated treatment program under which they will lose their license if they relapse. (O'Brien, Woody & McLellan, 1986) Similarly, parolees and probationers might be motivated to take naltrexone because they could lose their freedom and return to incarceration if they relapse. Making naltrexone or any other medication a requirement of parole or probation would require some assertiveness on the part of the judicial system which leads to the purpose of this symposium. Can judges offer heroin addicts the option to take a medication as a condition of their continued freedom or shortened sentence? Can the offender really make an informed decision under these circumstances? We have evidence (Cornish, Metzger, Woody, Wilson, McLellan, Vandergrift & O'Brien, 1997; Ling & Wesson, 1984; Capone, Brahen, Condren, Kordal, Melchionda & Peterson, 1986) that the result would be beneficial to the probationer although he or she might protest at the "loss of the freedom to get high." As indicated previously, there are some side effects associated with taking naltrexone such as upset stomach and headaches (Croop, Faulkner & Labriola, 1997) but these are not severe in most patients. In the recent, large controlled study of two doses of depot naltrexone compared to placebo, side effects were generally mild and only fatigue, nausea and decreased appetite occurred with a greater frequency than placebo. (Garbutt, Kranzler, O'Malley, Gastfriend, Pettinati, Silverman, Loewy & Ehrlich, 2005) This could

be translated into protests over side effects and would require training of prescribing physicians in the common side effects associated with naltrexone and their management.

Another question pertinent to the ethical use of this medication concerns the potential need for opiates if the patient is in an accident that produces pain or develops a painful illness. We have a long experience with naltrexone and these situations can be managed pharmacologically by other medications and by stopping naltrexone. (O'Brien, Greenstein, Mintz & Woody, 1975) Naltrexone would have no effect on anesthesia so that emergency surgery would not be affected. Nerve blocks such as those used in dentistry would not be impaired. Non-steroidal analgesics such as ibuprofen would not be affected. Only chronic use of opiates would be blocked. In the cases where other medications could not be used, high doses of opiates would be required until the end of the sustained release period. In practice and in clinical trials since 1973, this hypothetical situation has rarely been an issue.

In this context and for the sake of improving the nation's response to the heroin problem, it is important to ask: Why isn't naltrexone used more frequently? We admit we do not know the answers to this question – a reason for developing this special issue. What follows are a combination of our own speculations on this issue and some comments that may set the stage for the papers that follow in this issue.

Is it legal to mandate naltrexone as part of a probation sentence or a parole order – if so under what restrictions or conditions? Would mandating naltrexone be within the judicial powers as determined by the Constitution? There are judges who apparently fear that a mandated sentence or parole order is a violation of the civil rights of the individual offender. In this regard, it is interesting that in some jurisdictions, such as Alaska and

California, judges are already mandating naltrexone for DUI offenses.(National Drug Court Institute, 1999) Is this simply regional variation in judicial behaviors or a difference in statute across states? Apart from direct sentencing or other coerced treatment, is it wise, useful and practical to offer naltrexone as an option in drug courts; in plea bargaining; or as an option to obtain early release from prison?

Are the side effects associated with this medication a significant deterrent to mandated use? The controversy over hormone treatment of sex offenders comes to mind. Naltrexone does not produce a lasting change in the patient and it does not change their personality although it may reduce craving for heroin and alcohol. As suggested previously, the side effects associated with naltrexone are few, usually not severe and not persistent. Nonetheless, these questions come up regularly in these discussions, perhaps because so few physicians have heard of this treatment and few addiction treatment providers have made it available.

A proposal

From a public health perspective and with the benefit of over three decades of research on opiate addiction and opiate treatment, it appears that the most individually and publicly beneficial approach to the disposition of opiate addicted criminal justice involved individuals would be to offer the convicted, non-violent offender the choice of incarceration or probation that includes supervision, counseling and naltrexone. For similar individuals who are being released from incarceration, we suggest parole that includes supervision, counseling and naltrexone. Cases of serious additional psychiatric illnesses such as depression or schizophrenia – in combination with the opiate addiction -

would require psychotherapy and other psychotropic medications, in addition to the probation supervision, drug counseling and naltrexone.

In summary, and as a way of setting the context for the remaining articles in this special issue, we find that treatment with the opiate antagonist naltrexone to be effective, safe and very under-used. The soon to be available sustained release formulation of naltrexone should greatly increase its utility and even its effectiveness, as forgetting to take the medication will no longer be an option. We ask that the above proposal be considered by the criminal justice system as a means to rehabilitate a greater proportion of offenders with a history of opiate addiction. In the service of assisting debate and informed consideration of this proposal we have solicited some experts from the fields of legal, ethical and behavioral research as well as practicing drug court judges, probation and parole officers to consider the questions surrounding this proposal.

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