DRUG & ALCOHOL FINDINGS *Hot topic*

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GO Ethics and evidence on naltrexone treatment of offenders

Referring to long-acting naltrexone implants and injections, another hot topic explored the "curious possibility that precisely because a technology is (relatively) effortlessly effective, it is to that degree under suspicion". That was in relation to opioid use treatment in general; here we focus on convicted offenders, and ask: Are we missing a trick by not pressuring opioid-dependent offenders under supervision to take the pills or be implanted/injected with naltrexone?

Particularly for offenders, naltrexone seems the perfect medication for promoting abstinence from heroin and allied drugs – a pill taken daily or just twice a week which makes heroin use a disappointment rather than a 'high'. Free itself of psychoactive effects, naltrexone commandeers and blocks the neural receptors targeted by opiate-type ('opioid') drugs. A chemical instead of a physical shackle, it seems in tune with the deprivation of liberty imposed on offenders because it deprives them of opioid experiences rather than providing these in the form of substitute opioids. At its most optimistic, the hope and expectation is that long-acting naltrexone implants will result in patients "learning to abstain successfully", likened to learning to speak a foreign language fluently in that "It is not enough simply to know the foreign words, or the social and psychological techniques for resisting temptation. What matters is practice and the ability to use those words or techniques not just correctly and appropriately but automatically". However, lasting effects are not necessarily critical to treatment linked to a probation or parole order. Judges just need to be persuaded that treatment is likely to do as good a crime-prevention job as prison – that it will prevent or keep offending to a minimum for as long as the offender would have been locked up, rarely more than a year for non-violent drug-related offences.

Yet compared to substitute medications like methadone, naltrexone is rarely used inside or outside the criminal justice system. One reason is a limitation applicable to any medication which deprives patients of valued experiences: the more effective it is, the more patients simply refuse it or quickly abandon the treatment. Again this seems to make the treatment suitable for sentenced offenders, by definition already coerced into doing things they would not otherwise do. Let's examine this apparently suitable marriage between treatment and patient, and ask ourselves if by under-using it, we are missing what could be the most effective way yet to break opioid-dependent offenders of a crime-generating habit.

Overcoming resistance

There are at least three ways to overcome reluctance to start or continue with naltrexone. For convicted offenders, these could coalesce into a powerful treatment. The first way is technical – the availability of long-acting naltrexone products which once inserted in the body more or less consign the patient to a period when opiate effects are blocked; they cannot (or not easily) stop taking the medication, even if they want to. An implant inserted under the skin blocks opiates usually for two to six months; an intramuscular depot injection approved for medical use in the USA and Russia lasts about a month. From cell A3 we know that among treatment populations willing to try these products, they are more effective in preventing illegal opiate use than naltrexone pills which patients can simply stop taking, and also more effective than placebo versions of the implant or injection. In other words, at least while active they certainly can work for patients motivated to return to a life free of dependence on opiate-type drugs.

A major (but not absolute) impediment to using these products in the UK is that they have not been licensed for medical use. They can still be and have been prescribed (1 2 3 4), but patient and doctor have to accept the added responsibility of using a product which has not yet been certified as meeting the safety and efficacy requirements involved in licensing.

The second way to overcome non-compliance is psychological – to engender the motivation to take naltrexone by making it worth the patient's while in order to gain valued rewards or avoid aversive punishments. Third are social influences – the availability and commitment of someone with influence over the patient who is in a position to encourage them take the pills and monitor whether they do.

All three ways to prevent naltrexone being neutralised by non-compliance can in theory be marshalled for opioid-dependent offenders under criminal justice supervision. Long-acting implants or injections should be as available to them as to other patients, the prospect of early release from prison or avoidance of a more unpalatable sentence might be a powerful motivation-generator, while criminal justice officers – or treatment personnel reporting to them – can insist on frequent contact to bolster motivation and supervise administration of the pills or renewal of implants/injections.

But is it ethical?

However, because something can be done does not mean that it should be. With naltrexone ethical misgivings about pressuring people into treatment – ultimately aimed at benefiting not them but society at large – are sharpened by its potential danger. Any procedure which erodes opioid-dependent patients' capacity to tolerate high doses by successfully interrupting use of the drugs leaves those patients at heightened risk of fatal overdose if it does not also succeed in preventing relapse. Naltrexone may further aggravate the risk. Experts convened by the World Health Organization have warned that patients who stop naltrexone in order to resume heroin use can find that same ineffective dose they took hours before is later fatal as naltrexone levels fall and the blockade weakens. Some of the highest drug user death rates ever seen were recorded in Australia among patients who completed detoxification and tried to avoid relapse by taking oral naltrexone, findings explored in Effectiveness Bank analyses (1 2).

Post-detoxification overdose risk is one reason why UK national guidelines caution careful selection of patients fully committed to abstinence and with supportive and stable social environments available after discharge, among which may be seamless entry to residential rehabilitation. The preparation phase and the detoxification interlude itself should, said the guidelines, be used to bolster psychological resilience and social supports.

The problem is that heroin-dependent patients in general lack these kinds of supports, and convicted offenders may lack them even more, raising concerns about leveraging their restricted freedom to persuade them to accept naltrexone-based treatment. Part-funded by US government agencies, so prominent had this question become that in 2006 an issue of the *Journal of Substance Abuse Treatment* devoted a special section to "Mandating Naltrexone Among Court-Referred Patients: Is It Ethical?"

> *Naltrexone inserts tie the patient's hands, preventing them terminating the treatment*

Summarised here, the supplementary text (click to unfold 👁) explores these and other commentaries on the ethics of naltrexone treatment of offenders. You will see that there is generally agreement that given safeguards, it is ethically defensible to offer the choice of naltrexone-based treatment if this qualifies an offender for a more lenient sentence than would otherwise be imposed, such as early parole from prison or probation instead of imprisonment. This option has even been lauded as extending the offender's choices rather than restricting their autonomy. Still there are concerns that when treatment takes the form of a long-acting insert in the body which can be active for several months, it ties the patient's hands, preventing them terminating the treatment even if they find they want to, and that treatment has been subverted to criminal justice objectives rather than the good of the patient. Safeguards considered mandatory include what in societies with treatment systems like those of the UK would be a make-or-break condition – that naltrexone be just one of a menu of options which would include methadone or other substitutes for illegally obtained opiates. Since the great majority of opioid users would either choose no medication at all or methadone-type treatment rather

than naltrexone, this is almost certain to scupper naltrexone's chances with all but a few offenders.

In contrast to the Hobson's choice considered above, usually rejected as unethical is forced treatment over which the patient has no choice – not even of the usual sentence instead. But again there are dissenting voices, arguing that this might be acceptable as long as by restricting the patient's freedom to experience opioid effects, naltrexone extends their autonomy by freeing them from the cravings that constrict and dominate their life; "Infringing autonomy to create autonomy". Also the case was made that forced intervention is a more caring response than leaving the helplessly addicted to generate their own destruction and that of others: "Leaving … addicted people to their own destiny is not a 'no-fault' exercise for peers and for society at large. The self-destruction, incarceration, or disability of a family member does affect others." Counter-arguments are that the 'addict' retains their freedom to choose, and not having lost this, does not need it 'restored' by naltrexone, that the medication has not been shown to dampen cravings which lead to relapse when the treatment ends, and that this line of thinking would justify ignoring patients' wishes and forcing treatment on the over-eater or those exhibiting obsessive-compulsive tendencies – a slippery slope to state control via medicine displacing the (in Western cultures) valued autonomy of the individual.

Check out these powerful arguments by unfolding the supplementary text, preparatory to answering our final questions on where you stand on these controversial issues.

Close supplementary text

Kicking off the special section of the *Journal of Substance Abuse Treatment*, two researchers who had provided some support for naltrexone not only saw no serious ethical concerns, but recommended it as "the most individually and publicly beneficial approach" to opiate-addicted non-violent offenders when the alternative was being sent to or having to stay in prison. They pointed out its appeal to judges and probation officers, who may see methadone or buprenorphine as too similar to heroin itself, and to parolees and probationers who could be imprisoned if they relapse. Nowhere did they mention the risk of overdose if the patient does relapse after stopping naltrexone.

Without using these terms, the researchers said pressuring people to take naltrexone can actually extend their autonomy: "For the first time, they are able to move about their neighborhoods with no risk of heroin relapse. Some report this as a life-changing experience." In the same issue if the journal, medical ethicist Arthur Caplan centred on this aside from the researchers. Adopting a 'let's push the boat out and see if floats' tone, he argued that forced treatment over which the patient has no choice – not even of the usual sentence instead – might be considered acceptable as long as by restricting the patient's autonomy in this way, it extends it by "letting them be free from cravings, drives, and habits that inhibit their capacity to make choices" – "Infringing autonomy to create autonomy," was how he encapsulated it.

Though floated by a "well-known and widely respected" Emeritus Professor of Medical Ethics and Health Policy, this boat had some very large holes, responded two respected drug misuse researchers and commentators. Robert Newman doubted the efficacy of the treatment, but it was his more principled objections which hit home: the treatment was for the benefit of society not the patient, long-acting implants were inserted "for the specific purpose of rendering patients incapable of opting out, regardless of the subjective response(s) they may have to the medication", and if the treatment fails, it is the patient who pays the price of the imposition of a harsher sentence. Most fundamentally, the presumption that drug-dependent patients have impaired autonomy which can be restored by naltrexone is false; even in the throes of addiction, the individual remains able to take decisions and may refuse treatment on logical grounds, and after the grip of naltrexone has been released, the task of restoring autonomy remains because cravings persist or return. Even if forcing naltrexone on someone did lead them to adjust to an opioid-free life, this sort of justification "would allow one to ignore almost any decisions made by patients" well beyond the scope of addiction treatment.

This “slippery slope” argument was taken up by professor of psychology Frederick Rotgers in 2007 in a mailing list post. If bioethicists accept as a reality drug addicts’ reports of being unable to resist their urges, they also have to accept those of patients being treated for other compulsions, or illogically discriminate against drug users. It follows then that over-eaters or those with obsessive-compulsive disorders can also be medicated against their wishes, yet in the USA this is considered unacceptable. Why the difference? For professor Rotgers it was clear: in respect of drug use, “the primary aim of the mandatory medication is NOT the beneficent one of freeing the poor patient from his/her subjective compulsions to use drugs, but rather to protect the public from the criminal behavior supposed to be fuelled by addiction … The OCD sufferer, the binge eater, the bulimic, all have an ethically and legally protected right to refuse treatment. The addictive disease sufferer does not!”

In 2008, 13 doctors working in the USA saw it rather differently. From the point of view of the clinician faced with deciding whether to provide coerced treatment, their starting point was that in the USA, “for many addicts, the only way they will receive treatment ‘in spite of themselves’ is to end up in the criminal justice system, which is gradually evolving into an involuntary treatment system”. Apart from patient autonomy, for them “another central principle in medical ethics” was “beneficience … the duty of health care providers to be of benefit to the patient, as well as to take positive steps to prevent and to remove harm from the patient”. These principles sometimes conflict, but they placed most weight on beneficience, which may positively *require* the clinician to engage in coerced treatment: “failure to increase the good of others when one is knowingly in a position to do so (ie, to offer effective treatments) is morally wrong. As the evidence … suggests, coercive treatments are effective … it would be unethical to withhold [them from] patients who could benefit.” Bringing their case vividly to life, they argued that “Leaving addicted people to their own destiny is not a ‘no-fault’ exercise for peers and for society at large. The self-destruction, incarceration, or disability of a family member does affect others.” Objections on the ground of autonomy were turned on their head and criticised as “ally[ing] themselves with the coercive forces of the psychoactive substance” – the real autonomy-eroding villains, whose grip means an “addicted individual may have a compromised ability to make free, unencumbered choices. The autonomy perspective ignores the coercive forces of acute intoxication and withdrawal, subacute anxiety and depression, and chronic neurophysiological consequences of psychoactive substance use.”

A practical take on naltrexone implants came from Douglas Marlowe, a prolific and thoughtful researcher on addiction treatment and criminal justice supervision of drug dependent offenders. Writing in 2006 before much data was available, he thought implants more than worthy of study. Punishment has, he said, failed or been counterproductive, while offering rewards for good behaviour is generally unacceptable and gives the message that one behaves well only if it is rewarded. ‘Negative reinforcement’ in the form of early parole or diversion from criminal prosecution “offers a practical way to steer between these barriers by avoiding the iatrogenic [a ‘remedy’ which causes illness] effects of punishment and by being palatable to the citizenry”. Rather optimistically, he foresaw that because implanted naltrexone was “demonstrably efficacious, nonpsychoactive, and has few negative side effects … it would be unlikely to invoke the same types of legal and ethical objections that have traditionally been raised against the use of psychoactive medications with vulnerable populations of institutionalized offenders.”

Some of the arguments addressed so far relate mainly to forced treatment, but professor Marlowe was talking about the Hobson’s choice posed both in the UK and USA, when agreeing to naltrexone qualifies an offender for a more lenient sentence than would otherwise be imposed, such as probation instead of imprisonment or early parole from prison. Another article in the

special section of the journal argued that in these circumstances, naltrexone opens up options for the offender, actually extending their freedom of choice. Based on US law, his opinion was that "as long as the treatment is medically appropriate in the offender's case and … the offender has been fully informed about what is expected of him," these agreements should be legally acceptable and, moreover, to refuse to make this opportunity available would be to discriminate against opioid-dependent offenders. In contrast, when the offender would in any event be sentenced to probation or offered parole, insisting that this must incorporate naltrexone treatment could only be justified if for that individual it was essential to prevent criminality in the form of illegal opiate use, and we could be confident that it would achieve this objective – high hurdles given the availability of other treatments and naltrexone's slim research record with offenders.

From a British perspective, a criminologist specialising in substance misuse also broadly endorsed the ethical credentials of offering a choice between the normal sentence and a less restrictive one incorporating treatment. Basing his arguments on "international human rights law and leading codes of medical ethics," professor Alex Stevens also talked of the "opportunity" opened up by offering a treatment plus probation/parole package to drug-dependent offenders who otherwise face a more restrictive sentence, likely to be those convicted of relatively serious theft or other revenue-raising crimes.

But for professor Stevens, among the many conditions to be satisfied was that "the person is offered a choice between forms of treatment that are adequate and humane, according to his or her individual needs and wishes," and that treatment is the objective, not punishment. Experts commissioned by the World Health Organisation also said ethical treatment would entail offenders being offered a "range of treatments from which they can choose". Since substitute opioids like methadone have at least as good a record at preventing illegal opiate use as naltrexone, on these grounds it would be unethical to exclude these options if they are available within that society. Research tells us that given this choice, few would opt for naltrexone. This may be one reason why the treatment choices open to offenders sometimes consist of naltrexone or nothing. But another reason is that after perhaps initial 'testing' of the blockade, naltrexone promises to eliminate illegal opioid use in a way methadone does not, unless the doses are so high that 'on top' use is ineffective. Giving drug-seeking offenders lots of what they want free of charge in the form of the very type of drug which led them to offend rankles with some, no matter how effectively it curbs criminality.

Though as mentioned above it is legal to prescribe products which have not been licensed for medical use, the ethics of doing so have been questioned by a quartet including some of Australia's best-known drug misuse researchers. Australia is where a naltrexone implant was developed and in some areas widely used despite (as in the UK) not having gone through the normal process for obtaining a product licence for medical use. A heated issue in that country, in 2008 the critics argued that treatment-seeking opioid users "should be afforded the same regulatory protections as people with any other physical or mental disorder … Given the absence of data on safety and efficacy, it is of major concern that more than 1500 Australian opioid-dependent patients have been, and continue to be, given implantable naltrexone in the absence of its registration as a therapeutic good." Their argument would apply also to the UK: "We believe that it is currently ethically questionable for practitioners in any country to offer this treatment … outside the setting of

> randomised controlled trials". That last comment takes us to the trials which have been done – important not just to establish effectiveness, but also the ethical defensibility of pressuring offenders to accept naltrexone; there is general agreement that only if a treatment actually has a good chance of helping is there any possible justification for coercing or mandating its acceptance.
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> Close supplementary text

Does it work?

Given ethical concerns, no product licence, and the treatment's lack of appeal to many prospective patients, it is no surprise that both in the USA and the UK naltrexone is very much a minority option, even for offenders. In 2004, Dr Colin Brewer, whose private clinic provided long-acting naltrexone, recorded that despite "considerable benefits from probation-linked naltrexone," researchers evaluating court-ordered drug treatment in England found that only one offender in their sample had received naltrexone.

Another sign of how rarely this option has been used is that in 2006 a thorough search for randomised trials among offenders found just one dating from 1997 (it is listed above). A fresh search ending in 2014 found just three randomised trials. Even then the 1997 trial remained the most important test of naltrexone added to 'treatment as usual,' though it had been supplemented by a another US trial published in 2010.

These two trials are critical because they sampled offenders living in the community under criminal justice supervision, the main use envisaged for naltrexone. Both recorded marginally significant reductions in the proportions of offenders who violated parole attributable to adding an oral naltrexone programme to usual procedures. The later review found these results amalgamated to a clearly significant reduction. Parole violation was the only measure of criminality which could be amalgamated, but in the 2010 study there were others which gave a different picture – notably records rather than self-reports of parole violations (not significantly reduced) and the non-significantly but considerably more (32% v. 10%) naltrexone offenders charged with drug offences during the six-month follow-up.

These and other studies are analysed below unfold supplementary text. As a whole they show how few (previously) opioid-dependent offenders opt for naltrexone even when opioid substitutes are not on offer, that when naltrexone administration is supervised, and when offenders want it, have strong incentives to comply, and the treatment is active, it helps suppress opioid use and prevent parole or probation violations, affording offenders opportunities for learning to live opioid-free in the community which may otherwise be denied them. Without these conditions, rejection and drop-out from the programmes becomes the norm. Even with them, there seems no evidence that the substance use and parole/probation violation gains made while naltrexone is active persist after treatment ends, or (perhaps related) that they automatically extend to the stabilisation and improvement of other aspects of the patients' lives.

As with the ethical considerations outlined above, check out these findings in greater detail by unfolding the supplementary text, preparatory to answering our final questions on where you stand on naltrexone treatment for

offenders.

Close supplementary text

Published in 1997, the first randomised trial of naltrexone for opiate-dependent offenders (listed above) recruited 51 of 300 potentially eligible offenders on probation or parole and being supervised by the substance abuse arm of the federal probation service in Philadelphia. Nearly all the rest declined this better-than-even chance (by design, twice as many offenders were allocated to naltrexone as to the control group) of extra support to stay opiate-free. The 51 were randomly allocated to fairly intensive weekly contact with their probation officers during which they would be urine tested, or to this plus twice-weekly naltrexone administered by researchers in the same building and at the same time as one of their probation appointments. The researchers also urine-tested the offenders, the results of which were kept confidential. Though over the six months of the follow-up a higher proportion of naltrexone patients were retained in the study (52% v. 33%), on average they were much less likely (8% of tests v. 30%) to test positive for opiates – a statistically significant difference unlikely to be due to chance and attributed to the naltrexone supplement. There were no signs that naltrexone-blocked offenders had compensated by switching to other drugs. Greater rates of non-attendance and illegal drug use probably contributed to fact that over the six months, 56% of the probation-only offenders were sent back to prison for violating probation but just 26% also administered naltrexone, another statistically significant difference. The study exemplifies the conclusion that naltrexone has a role among closely monitored patients who have much to lose (in this case, their freedom) from dropping out of treatment and returning to opiate use, especially when pill-taking is supervised – but also indicates that even then, few offenders may opt to have their freedom to use opiates pharmacologically curtailed.

The contrast between findings in this study and one published in 2010 illustrates the importance of monitoring. Encouraged by their earlier findings, the same research group tried psychosocial treatment with versus without naltrexone for opiate-dependent offenders under legal supervision in the community, though this time they were all already in intensive treatment for their drug problems. As before, over an intended six months of treatment and follow-up assessments, the drug was administered twice-weekly by the research team, but at a slightly higher dose (totalling 300 mg a week rather than 250 mg). In both the naltrexone and the no-naltrexone groups, just under a third of patients completed treatment; final assessments could be made on fewer than 40 of the 111 participants. On crime there was a mixed picture. Naltrexone did not significantly affect recorded criminality, though non-significantly more (32% v. 10%) naltrexone offenders were charged with drug offences. Favouring naltrexone, the offenders' own accounts indicated that with naltrexone they were significantly less likely to have violated parole. When it came to drug use, while retained in treatment the

naltrexone patients submitted significantly more opiate-free urines, indicating that relapse to opiate use was substantially more common without the support of naltrexone. However, once missing tests were assumed indicative of opiate use, this result was overwhelmed by the high drop-out rate; naltrexone still had the advantage, but it was no longer statistically significant. By the end of the six months no significant differences remained in opiate use, even among patients still in treatment.

With or without naltrexone, in this study it seemed that the minority of offenders who completed treatment rarely used opiates. In contrast, before they left, naltrexone helped the majority who later dropped out to stay opiate-free. Reading between the lines, offenders who were predisposed to return to opiate use were helped by naltrexone as long as they stayed in treatment, while those more 'compliant', stable, and determined to complete treatment, did not need this support.

When the researchers asked themselves why the results were less convincing than in their earlier study, they highlighted the much lesser degree of criminal justice supervision and consequently the lower risk of non-compliance being spotted and resulting in sanctions. In the later study, only among the relatively closely supervised and regularly urine-tested offenders referred from a drug court did naltrexone help patients complete treatment – 57% did so compared to none not administered naltrexone, though numbers were small. The practice implications were that "in order to be successful, oral naltrexone in probationers and parolees requires more supervision than is typically available in the criminal justice system". Neither of the reports on the trials documented non-fatal overdose events or deaths.

Prison and compulsory detention

Turning from community supervision to prisons, what seems the only remaining randomised trial using the oral form of naltrexone among offenders was conducted in Australian prisons between 2002 and 2004. Consenting prisoners were randomly allocated to oral naltrexone, methadone maintenance, or drug-free counselling. Arrangements were made for free-of-charge continuation of naltrexone after release. Nevertheless the trial foundered on the unwillingness of the prisoners to actually take naltrexone. Only 9 out 66 assigned to the treatment started naltrexone and only 14 out of 204 opted for the treatment over the entire two-year study period; of those, just one stayed in treatment for six months, far worse figures than for methadone. For the researchers, the most likely explanation for the findings was that "inmates were not subject to coercion or incentives to enter and stay on naltrexone

maintenance. In the absence of such incentives, opioid dependent inmates showed a preference for agonist treatment including methadone maintenance and buprenorphine maintenance. Many inmates who achieved abstinence preferred no treatment or drug free counselling over naltrexone. The overall conclusion of the study was that poor patient acceptability and retention did not support oral naltrexone in this treatment group."

Randomised trials have been supplemented by studies of how supervised offenders respond to naltrexone in normal practice. Listed above, the first documented use of naltrexone among offenders appears to have been in Nassau County Jail in New York state in the USA, where from 1972 a work-release programme began to accept opiate-dependent inmates as long as they agreed to take oral naltrexone (1 2 3 4; unclear whether paper 4 involves offenders). Prisoners in general were already allowed out to work, earn and save money, but previously opiate-dependent inmates had been excluded because they "may be tempted to get high when faced with old friends and familiar situations". Monitored administration of naltrexone generally twice a week plus random urine-testing was seen as qualifying them for work-release privileges because (perhaps after a few attempts which were not heavily sanctioned) it would prevent them giving in to temptation.

Blocking was, however, not seen as a complete solution. At the same time extensive support was provided to overcome dependence and reintegrate into society, including weekly counselling, vocational rehabilitation assessments, possibly financial support for training, pre-release referrals and community contacts, and help with finance, employment, family relationships, legal issues, and finding appropriate treatment. To aid the latter patients were often taken round the neighbouring naltrexone treatment clinic. About a fifth continued their treatment on release.

Though accepting that the opposing approach of prescribing opioid substitutes also has its place, according to officials from the county's Department of Drug and Alcohol Addiction (citations above), the net result was that "The addicted inmate is provided access to correctional program options that were previously out of reach, including the possibility of firmer anchoring to family and other aspects of life in the community." From being excluded and as too high a risk, naltrexone-treated participants were found to transgress or drop-out no more than

other work-release prisoners: “The correctional administration now views naltrexone program participants as among the most trustworthy in the facility.”

Like the New York programme, one in Singapore did not penalise initial lapses to heroin use because these were considered potentially valuable learning, demonstrating to the patients that heroin use was pointless while taking naltrexone and ‘extinguishing’ conditioned responses associating heroin use with rewarding experiences. Supervised consumption of oral naltrexone was added to an existing programme which detained opioid-dependent adults in a rehabilitation centre and after a year monitored them in the community. Release from the centre could be obtained in six months instead if patients opted for a year on naltrexone. Of those who did, three-quarters were retained though the first year of the community phase of the rehabilitation compared to about a quarter in the preceding three years when naltrexone was not on offer. By the end of the following year when naltrexone treatment had stopped but drug testing continued, 32% were still thought free of opioids. Fears of serious side-effects from naltrexone proved unfounded, and the report does not mention any overdoses among the adverse events recorded.

In Bristol in England a drug treatment service mounted a naltrexone programme for prisoners who had been using both crack cocaine and heroin. The intention was to use both oral and long-acting forms of the drug but in the event only the oral form was available. An evaluation found that 172 referrals led to just 51 patients being inducted on to naltrexone, of whom only eight completed three months on naltrexone and two nine months. A major impediment was the inability to induct most of the referrals while still in prison. When induction was delayed until after release just a quarter took up the opportunity, possibly partly because the induction clinic was not conducive to abstinence-oriented treatment. In contrast, 9 of the 10 inducted in prison continued treatment on release. Lacking coercion or rewards for compliance, it is unlikely that the programme would in any event have succeeded with other than a minority of offenders, but any chances it had were stymied by work pressures and organisational shortcomings in both prison and clinic.

Long-acting naltrexone

Like the earlier US studies, a US trial listed above compared usual procedures (in this case drug counselling) to these

supplemented by naltrexone for offenders with a history of opioid dependence who were living in the community under criminal justice supervision. The major difference was that naltrexone was in a long-acting form injected into the body, whose effects last about a month. Another difference from earlier studies was that only offenders who said they preferred opioid-free treatments like naltrexone to opioid-maintenance treatments like methadone were allowed to join the trial. Across five sites and over nearly five years, 308 offenders were randomly allocated, on average about 13 per site per year, perhaps indicative of naltrexone's niche applicability. Over the 24 weeks of treatment the intention was to renew the injections every four weeks. Among this sample selected to be friendly to the treatment, 77% of intended administrations were completed. During the treatment phase the proportion of participants who relapsed to a period of opioid use was 43% aided by naltrexone and 64% without; other measures consistently confirmed a naltrexone-aided reduction in opioid use. However, these impacts were no longer apparent between six and 12 months after treatment ended. Neither during treatment was there any impact on reimprisonment rates. Importantly, there were no overdoses among the naltrexone patients including periods after treatment had ended, but 12 in the usual-treatment comparators.

A non-randomised pilot study at the same sites also seemed to recruit few participants. The site which made the largest contribution recruited 35 out of 336 potential participants. Across all five sites there were 61 participants. At the sites where this was the intended regimen, four in ten of the offenders under criminal justice supervision completed all six monthly injections of long-acting naltrexone and on average four of the six injections were administered. Just one of the 26 offenders who completed their treatment tested positive for opioid use at the end of the six months of treatment.

Another non-randomised study was based on routinely collected records of how patients with alcohol and/or opioid use problems progressed after agreeing to different treatments while under community supervision by the criminal justice system in the US state of Missouri. Among offenders who chose or agreed to it, long-acting naltrexone seems to have helped support an improvement in rates of abstinence from alcohol and other drugs over three times that for psychosocial treatment only, over four times that for oral naltrexone, and over

10 times that for buprenorphine maintenance. There was, however, no evidence that long-acting naltrexone was associated with fewer arrests or more patients gaining employment. These findings remained after adjusting for known and unknown differences between the patients who received different treatments, but nevertheless they could at least partly reflect pre-existing differences in the offenders who entered the different treatments or in their situations, especially the likelihood that those committed to abstinence were routed towards and/or were prepared to accept naltrexone injections. Whether long-acting naltrexone's advantage remained after treatment ended was not reported.

Leaving prison

Released in 2015 were the findings of a trial of long-acting naltrexone administered in jail immediately before release plus renewal four weeks later, an attempt to prevent the typically rapid (and dangerous) relapse to opioid use among formerly dependent prisoners. That it took over three years to find the 34 prisoners in New York City's jails who joined the study, and that no women could be included, seems to indicate that among prisoners who have access to methadone and allied treatments, the demand for long-acting naltrexone is small – participants could neither be in nor planning to enter methadone or buprenorphine maintenance treatments.

All 34 trial participants were offered brief counselling and referral to treatment services, and 17 were randomly allocated to the additional naltrexone programme. All but two of the 17 allocated to naltrexone were injected with the drug. One was retained in prison, leaving 16 who could be assessed after release. Of these, 12 also accepted the second injection. During the first four weeks after release, 15 of the 17 (88%) no-naltrexone offenders had relapsed to opioid use compared to just six of 16 (38%) offered naltrexone, a large and statistically significant advantage for naltrexone unlikely to have occurred by chance. Across the eight post-release weeks assessed by the study, over 90% of no-naltrexone patients relapsed compared to half offered naltrexone. The results showed that among (formerly) opiate-dependent prisoners prepared to accept this treatment, and for whom maintenance prescribing is unwanted or unavailable, long-acting naltrexone is greatly superior to usual care in preventing return to regular opioid use in the weeks immediately after release. Additional

recovery support was offered to the naltrexone patients before their release, which may also have partly accounted for their doing better on release. A worrying finding was that many more former prisoners offered naltrexone injected drugs after release from prison – 25% versus 6% of the no-naltrexone control group. Also, slightly more had used cocaine (56% versus 47%) and only slightly fewer had been returned to prison (31% v. 41%). Given the small size of the sample, none of these differences were statistically significant, but they do seem to suggest that while they restricted use of heroin or other illegal opioids, naltrexone injections did not control other forms of drug use and did little to stabilise other aspects of the patients' lives.

The US trial described above tested naltrexone injections against no medication rather than against what may be considered the 'gold standard' approach of offering methadone or buprenorphine maintenance in prison and seamlessly continuing it on release. However, a Norwegian study did make this comparison. In the month preceding their release date, prisoners dependent on opiates before their sentences were randomly allocated either to methadone maintenance or to a naltrexone implant whose effects last for six months. Of the 111 inmates who qualified for the trial, most refused to participate, usually because they intended to build on their enforced break from opiates by remaining abstinent on release. Of the 44 who did join the trial, just 11 started methadone treatment in prison and 16 were implanted with naltrexone (seven of the 23 allocated to naltrexone refused implantation). Compared to before their imprisonment, across the 44 offenders on average in the six months after release use of heroin and illicit benzodiazepines had fallen substantially, but not by significantly more among those allocated to methadone versus naltrexone.

Even if long-acting naltrexone and methadone are of equivalent effectiveness among those prepared to be randomised to either treatment, methadone is likely to be more acceptable to greater range of opioid-dependent prisoners. Unless incentivised in some way – for example, by offering early release – it seems likely that naltrexone injections will be accepted only by prisoners who, though dependent on opiate-type drugs before their sentence, are prepared to commit to a month without being able to experience the effects of these drugs, yet are not confident they can resist re-addiction on leaving prison – an unusual combination. An often false confidence in their

> determination and ability to build on prison by starting an opioid-free life on release leads many patients to reject medication of any kind.
>
> Close supplementary text

Guidance

Efficacy and ethical considerations should come together in guidance for practitioners and service planners, but in the UK there is no guidance specific to offenders. Last published in 2017, the so-called 'Orange guidelines' for clinicians involved in treating problem drug use said of naltrexone:

- Among highly motivated patients provided with adequate supervision, naltrexone can help to maintain abstinence.
- Naltrexone should usually be used only after a patient is opioid-free (verified by testing for the presence of opioids).
- The impact of naltrexone may be enhanced by additional support from a keyworker or group, allowing service users to discuss any issues related to sustaining abstinence.
- Its effectiveness should be reviewed regularly and if opioid use becomes apparent, discontinuation of naltrexone should be considered.

In this the guidelines echo recommendations from Britain's National Institute for Health and Care Excellence (NICE) that the drug is suitable for detoxified patients who are highly motivated to remain in an abstinence programme, and should be administered under adequate supervision as part of a programme of supportive care to people who have been fully informed of the risks. Despite an unpromising record among the generally randomly allocated patients in clinical trials, NICE's experts were convinced that among selected individuals and in the recommended circumstances, naltrexone can greatly aid abstinence from opiate-type drugs with associated improvements in the patient's quality of life. The World Health Organization is clear that the post-treatment overdose risk means naltrexone is best reserved for patients who have a reasonable chance of remaining abstinent, and that those severely dependent should be cautious about embarking on the treatment.

Specifically in relation to long-acting products, an Effectiveness Bank hot topic concluded that the clearest candidates for naltrexone implants and injections are patients motivated to return to a life without opiate-type drugs, who have the resources, stability and support to sustain this, are unlikely simply to use other drugs instead, but who when free to experience opiates, cannot resist them. Long-acting formulations may also be considered for

unstable patients at very high risk of overdose, but who will not accept or do poorly in substitute prescribing programmes. Other candidates might include those unwilling or unable to accept daily supervised consumption if this is a requirement of being prescribed substitute medications.

Unresolved questions

This introduction to the ethics and effectiveness of naltrexone treatment for offenders has raised but not resolved questions for you to ponder, including: Is it OK to force this treatment on the unwilling in their own interests and that of their families and the broader society, because once freed of their addiction, this will extend the patient's autonomy rather than restrict it? Or only OK if the offender can choose naltrexone as part of a less onerous sentence than they would otherwise have been given? Do we have enough evidence that naltrexone-based treatment works to feel comfortable about pressurising *anyone* to accept it? Should we also offer better established alternatives like methadone maintenance, even if this means naltrexone will rarely be chosen, and even if methadone-maintained patients commonly break the law by taking heroin once in a while? Are we missing a trick by not more widely forcing or pressuring opioid-dependent offenders to take naltrexone under supervision or to be fitted with long-acting implanted or injected naltrexone products? These products, after all, force an interruption in regular opioid use which may not be achievable by any other feasible means, and which could be used to embed opioid-free ways of coping. Or is this an ethically and perhaps also physically dangerous subversion of treatment to criminal justice ends when medicine is supposed to prioritise the patient's welfare? But perhaps this is – despite their contrary wishes – the best way to safeguard some patients' welfare, rather than leaving them (and those around them) to descend deeper into a destructive addiction – like forcibly holding back someone about to walk off the edge of a cliff, *even if that is what they choose to do*?

> *Like holding back someone about to walk off the edge of a cliff – even if that is what they choose to do*

Thanks for their comments on this entry to Colin Brewer, a psychiatrist based in England. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

Last revised 15 August 2018. First uploaded 15 August 2018

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