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title = 'Trigger search for relevant documents. Opens new window' target='_blank' onClick='HCEvent('naltrexone_opiate.hot',1);'>Opiate-blocking implants: magic bullet or dangerous experiment?

For some a magic bullet, for others, an unsafe experiment with human beings as the guinea pigs, naltrexone implants and injections block the effects of heroin for weeks or months. Naltrexone is an opiate antagonist which in itself has no psychoactive effects, but commandeers the neural receptors targeted by opiate-type ('opioid') drugs. The implant form 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. Both avoid the need to take medication daily, in theory overcoming the main shortcoming of oral naltrexone – that patients usually stop taking the tablets and resume heroin use.

We'll see that while no instant solution, these preparations represent a valuable extension to the range of interventions suitable sometimes for some people depending on their characteristics and circumstances – in particular, those ready for abstinence from opioid drugs. As with other approaches, the social and psychological adjustments needed to stabilise a non-addicted life are likely to take time and require help which goes beyond medication, though this can help create the space for such adjustments.

Guidance reflects concerns over safety and efficacy

In the UK, neither implants nor depot injections of naltrexone have been licensed for medical use. They can still be (and have been – 1 2 3 4) prescribed, but patient and doctor have to accept the added responsibility of using a product which has not yet been shown to meet the safety and efficacy requirements involved in licensing.

That too is the situation in Australia, where controversy over implants is at its height, one front in the bitter battle between the supporters of harm reduction and methadone, and those who see abstinence from legal and illegal opioids as the route to recovery. Fuelling the controversy is widespread implant administration by some clinics in ways which both

an advisory body set up by (and in 2014 de-funded by) the national government and the doctors' national association believe circumvents regulatory procedures intended to assure quality, safety and efficacy. In 2012 the association found this "ethically problematic as it puts patients at risk of unknown harms, for an unknown benefit". Rather than being provided routinely, the doctors said such untried medications should be reserved for patients facing impending death. After reviewing the literature, the year before the Australian government's National Health and Medical Research Council had judged that naltrexone implants "remain an experimental product and should only be used within a research setting".

In the USA, two years after its approval for opioid dependence and six after being approved for alcohol, in 2012 federal health service guidelines did not portray injectable naltrexone as a last resort, but as one option among others suitable for a range of patients. By 2015 guidance on treating opioid addiction from the American Society of Addiction Medicine was even more relaxed about the risks, warning about post-treatment overdose in almost exactly the same terms for the mainstream medications methadone and buprenorphine as for naltrexone. A sign of its acceptance in criminal justice circles, at the end of 2015 it was reported that around 100 US jails and prisons nationwide offered departing inmates injectable naltrexone to reduce rates of re-addiction and re-incarceration.

Exposes philosophical divides over the nature of addiction

Aggravating concerns is the fact that commonly implants or injections are used after and in conjunction with the precipitation of withdrawal from opiate-type drugs while patients are anaesthetised or sedated. On safety grounds,British guidelines say the more radical of these procedures entailing anaesthesia or deep sedation "must not be offered", though lighter forms of sedation are seen (1 2) as having a useful role while being less risky.

Tarnishing long-acting naltrexone with the risks of any preceding sedation or anaesthesia would be unfair; in practice and in theory the procedures are distinct and separable, long-acting naltrexone commonly being offered after conventional detoxification, and rapid detoxification often being followed by oral naltrexone. However, there is an affinity between the two procedures which both use medications to eliminate the patient's freedom to experience opiate-type drugs. Especially when used together, they raise philosophical issues over the nature of addiction and its treatment. Withdrawal while sedated or unconscious followed by naltrexone implants or injections promises a painless technological fix to heroin addiction, within a day ridding the patient's body of opiates and then for months preventing further use, confounding understandings of addiction as a deeply rooted psychological and social condition requiring life-transforming change. It was this contradiction which the president of the Massachusetts branch of the American Society of Addiction Medicine had in mind when she said of injectable naltrexone, "Its reputation on the street is that it's a silver bullet ... But there is no way to heal from addiction without doing the psychological work of recovery."

Such cautions imply that when an addict is suddenly denied opiate-based amelioration of their life problems, these problems will be expressed or handled in some other way, such as resort to non-opiate drugs, attempts to extract the implants, or severe psychological distress. Add in the lack of official sanction from regulators and in some circumstances the high cost to sometimes desperate patients and families, and the mix is one which arouses passions and exposes philosophical divides between those who see addiction as a neural disorder amenable to technical 'fixes', and those who see it as a whole-life pathology.

Lined up to reinforce these positions are practical and safety considerations which the two sides see very differently.Proponents argue that long-acting naltrexone offers a lifeline for addicts otherwise facing possibly years regularly attending methadone clinics, one grasped by thousands when it is made available, but one which pharmaceutical companies see as

unprofitable. Especially without the backing of big companies, seeking and awaiting the procedure's official approval would, they argue, have denied this opportunity to patients and families. Sceptics see the enthusiastsas blinded by evangelical zeal, contending that that even apparent lifelines need testing and approval before addicts are diverted from proven approaches like methadone, which at least keep them alive and stable.

Further obscuring the issue of whether the procedure works is the allegedly substandard practice at some clinics offering this treatment, tarnishing the treatment itself with the shortcomings of its delivery vehicle. In relation to one clinic headed not by a doctor but a psychologist, after the death of three former patients in 2012 the *Sydney Morning Herald* reported "damning findings by the state coroner and adverse evidence in three different disciplinary tribunals of the medical, nursing and psychology professionsrdquo;. The coroner's report was scathing, counterpointing the "highly expensive" treatment with the impression that the clinic was "run on a minimal expense basis". Though the spotlight was more on rapid opiate detoxification than naltrexone implants, the report suggested both procedures have been implemented with inadequate assessment and follow-up care.

Evidence limited but so far reassuring

Excess overdose deaths are the prime concern over oral naltrexone, and on this score the long-acting versions have a reassuring record. As expected, studies of naltrexone implants have found these protect against opiate overdose while they are active, but also that overdose reductions have outlasted the active periods of the implants. Among caseloads prepared to accept this treatment, long-acting naltrexone seems a major advance on oral naltrexone in safety and effectiveness in curbing illicit opiate use. However, this could partly be due to the weakness of the psychosocial supports provided along with oral naltrexone. When these were substantial, a US report found that still the high-dose, long-acting injection had an appreciable overall advantage, but one which was due to impacts on the less severely dependent patients. The more highly dependent actually did better with the intensive support offered oral naltrexone patients. Though lapse to using opiate-type drugs was common, after this possibly disappointing experience, patients administered injectable naltrexone usually stopped using, while oral naltrexone patients stopped attending for treatment.

Some studies (1 2 3 4 5) have shown that concerns that patients would try non-opioid drugs as a way of sidestepping the naltrexone blockade have some validity, others the opposite (1 2). Importantly, there are few reports of patients taking dangerously prodigious quantities of opiates in attempt to override the blockade.

These results though derive from a literature which is both small and methodologically weak. Reviewing it in 2010, the Australian government's National Health and Medical Research Council remained unconvinced of the safety or effectiveness of the implants, and was not reassured about the long-term overdose risk after treatment has ended.

In particular, randomised trials have been rare. They include a Russian study comparing long-acting injectable naltrexone to an identical placebo as a way of sustaining abstinence after inpatient withdrawal. The active medication was much more effective at suppressing opioid use. Far more so than placebo patients, naltrexone patients had also reduced their risk of infection and experienced improved health and quality of life. Particularly promising was that nearly 60% of naltrexone patients were prepared to repeat the four-weekly injections over the full 24 weeks of the study. But even in this relatively promising caseload, for nearly half the patients, naltrexone injections and infrequent counselling were insufficient to retain them in effective treatment.

The Russian trial was made more feasible by the absence of substitute prescribing programmes, leaving varieties of opioid-free treatments the only alternatives for patients.

In Norway, substitute prescribing is available, but restricted, creating another environment within which randomised trials are more feasible. One trial similar to the Russian trial also delivered similar findings, but in respect of the six-month implant. Despite a highly selected and probably highly motivated caseload, over half the implant patients tried resuming opioid use. Though the implant was expected to render such use futile, repeated use did happen: on average the 12 of 23 followed-up implant patients who used opioids had used these drugs on about 38 days out of the roughly 180 days of the study. They did, however, use much less often than comparison patients, and the figures were skewed by some very frequent users.

A sister study (1 2) from the same research team in Norway randomly allocated prisoners dependent on opiates before their sentence to naltrexone implants or methadone maintenance to promote continuity of treatment on release and avoid relapse. Generally neither was acceptable to the prisoners, who felt (often falsely) that they could avoid relapse on their own. Among the minority who did participate in the study, in the six months after release crime and substance use reductions were not significantly greater with implants than with methadone.

A criticism of these and other trials to date is that they have included highly selected patients. However, in this they may have reflected normal practice. Patients will only opt for such procedures if they are prepared (irreversibly in the case of depot injections) to commit to possibly weeks or months without the effects of heroin or other opiate-type drugs. From patients in naltrexone implant/depot studies *not* allocated to these drugs, we know that even in these caseloads, treatment drop-out and relapse are common. Long-acting naltrexone helps these patients sustain their resolve.

A limitation of the studies is that only the better clinics are likely to invite researchers in or cooperate with their work. Those (for example, in Eastern Europe) which tempt UK-based addicts with low-cost detoxification and naltrexone implants, but are in no position to offer psychosocial aftercare, also cite no studies in their favour. What happens to patients after they visit these clinics is unknown, and if it were known, might paint a less reassuring picture of the overall safety and effectiveness of the procedure.

Who benefits?

The clearest candidates for the treatment are patients who are motivated (perhaps due to employment or other pressures) to return to a life without opiate-type drugs, and who have the resources, stability and support to sustain this, are unlikely simply to use other drugs instead, but who when free to experience heroin and allied drugs, cannot resist using them, possibly reflected in their poor compliance with oral naltrexone treatment. Whatever treatment is tried, it should be possible for patients to quickly and painlessly revert to or try another if it does not work out.

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.

US guidelines also suggest that people facing a time of severe stress or other relapse-precipitants may benefit from the reassurance of the blockade. In line with experience in Britain, the guidelines also highlight the injection's suitability for young adults, likely also to meet the criterion of having a short or less severe history of dependence, and for methadone maintenance patients who perhaps after years are stable enough to want to end their dependence on methadone, and to have a good chance of doing so.
Later guidance from the American Society of Addiction Medicine simply says the injectable

formulation is especially suitable for patients not in a position to or unwilling to regularly take naltrexone tablets.

There are obvious reasons to be discriminating in the use of these medications. If opiate-type drugs are supports relied on by vulnerable individuals, naltrexone implants and injections suddenly remove this support, and make it virtually impossible or difficult quickly to resurrect it. Some patients can find replacement supports or sources of resilience, others will flounder and fall. Undiscriminating advocacy of the kind which alarmed an Australian coroner is clearly poor practice in respect of any medication. Guidance is universally keen to emphasise that implants and injections are not insert-and-go solutions. As with methadone, patients should be regularly monitored, and those who need this, supported to make the relapse-preventing life changes made possible by a medication-aided space free from preoccupation with obtaining and experiencing illegal opiates.

Thanks for their comments on this entry to Nikolaj Kunøe of the University of Oslo in Norway, Duncan Raistrick, formerly Clinical Director at the Leeds Addiction Unit in England, and Colin Brewer of the Stapleford Centre, also in England. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

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Nltrexone implants