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▶ Favorable mortality profile of naltrexone implants for opiate addiction.

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Few treatments for opiate addiction arouse as much controversy as naltrexone implants. Inserted under the skin, these block the effects of heroin for up to several months - for some, a magic bullet, for others, an unsafe and ethically dubious experiment. More evidence from Australia that the overdose death risk is less than with oral forms of the drug.

Summary At an Australian addiction treatment clinic the death rate of opiate-dependent patients treated with the heroin substitute buprenorphine between 2000 and 2007 was compared with those treated with implants of naltrexone which block the effects of heroin and allied drugs for up to several months. During this time 2518 patients were prescribed buprenorphine free of charge (though there were pharmacy charges) and 255 were implanted, mostly at their own expense. Records were matched with those of deaths recorded by the registrar of the relevant Australian state.

Main findings

Four naltrexone and 43 buprenorphine patients were known to have died. There were no deaths while a naltrexone implant was active but four among patients at times when the implant would no longer have been effective, resulting in an overall death rate of 3 deaths per 1000 years the patients had been tracked. For buprenorphine, the corresponding figure was 5.35, largely due to 40 deaths during times when the patients were not being prescribed the drug. Not only was the overall death rate lower among naltrexone patients, but this was also generally the case in each age band. All but one of the four naltrexone deaths occurred several months after the implant would no longer have been effective.

The authors' conclusions

The major finding of the current study was that in terms of death rates, naltrexone implants compared favourably under most comparisons: with the same clinic's experience of buprenorphine, with the Perth methadone programme, and even with Australian national population age-adjusted death figures. This was the case despite the fact that buprenorphine is a treatment widely recognised as safe and effective.

Another important finding was the utility of long-acting forms of naltrexone implants to promote treatment retention in a group of patients who tend to avoid traditional indefinite substitute prescribing programmes.

FINDINGS As with any abstinence-based treatment, relapse risking overdose due to lost tolerance to opiate-type drugs is a serious concern after naltrexone implants have lost their effectiveness. However, studies of naltrexone implants have found these not only protect against overdose while they are active, but also that opiate overdose reductions have outlasted the active periods of the implants. The featured study is in line with this literature, which together suggests that − among caseloads prepared to undertake these procedures − long-acting implant and injectable forms of naltrexone are a major advance on oral naltrexone in safety and effectiveness in curbing illicit opiate use.

These results derive though 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. Their conclusion was that implants should "only be used in the context of a well conducted [randomised controlled trial] with sufficient sample size, appropriate duration of treatment and follow up, regular robust monitoring, provision of a comprehensive psychosocial treatment [programme], and with comparison to current best practice".

A criticism of trials to date is that they 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.

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 including prescribed substitutes, 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 regimens. The treatment 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.

As the featured study hints, it would not be justified to conclude from its findings that for any given patient or across a population, naltrexone implants which block heroin's effects are safer than buprenorphine which substitutes for heroin. Substitute prescribing, which

'goes with the grain' of the patient's addiction, has mass appeal. Without it, many addicts would not enter treatment, especially if the step had to be as steep as from opiate use several times a day every day, to no opiate use (or at least, no effective use) for months. Different kinds of patients are attracted to and suitable for these different treatments; they might also have differed in their life expectancies even without treatment, and forced to accept the other option, might not have done as well as patients who chose it and/or were considered suitable.

In the featured study in particular, implant patients were the minority prepared not just to accept, but willing and able to pay for a procedure which would mean they could not experience opiate-type effects for up to several months. Additionally, buprenorphine patients spent very little time in treatment – just 14% of the time from when they started to the end of the study period. As detailed in another report on the same patients, at just 16 days the typical treatment duration on buprenorphine is suggestive of poor retention, and on average the patients were in and out of treatment three or four times. Retention was particularly and significantly worse among the buprenorphine patients who died. Counselling was offered, but not at the prescribing clinic, and few patients took up the offer. It seems likely that at this clinic the buprenorphine comparator was not implemented in a sufficiently supportive way to hold patients in treatment and exert the full protective effect. Set against this, long-acting naltrexone implants virtually ensured retention in an active pharmacotherapy for up to several months.

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) used, but patient and doctor have to accept the added responsibility of a product which has not yet been shown to meet the safety and efficacy requirements involved in licensing.

Naltrexone implants and depot injections impede opiate-based pain relief. This is a greater problem with the irreversible long-acting naltrexone injection than with implants which can be removed. Possible adverse effects of naltrexone on liver function are also a concern based on early studies, but not one confirmed in several later studies.

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