MATTERS ARISING

Opioid overdose deaths can occur in patients with naltrexone implants

A recent report of five people who had received naltrexone implants and later died of drug overdose has attracted substantial criticism of the case selection and conclusions. ***(MJA 2007; 186: 152-153)***

Gary K Hulse and Robert J Tait

To the Editor: Gibson et al provide us with five cases of fatal drug overdose in an article titled "Opioid overdose deaths can occur in patients with naltrexone implants".[1]

Three of these people did not have an active naltrexone implant — two of the deaths occurred 6 months after implant insertion (which is the outer limit of the longest duration implant available), and the implant had been removed from the third person.

This leaves only two cases.

In one of these, the cause of death was combined non-opioid drug toxicity, including amphetamine and a cocktail of other drugs, where opioids were not present. Obviously, naltrexone, an opioid antagonist, will not protect against non-opioid drug overdose.

Clearly these four cases should never have been included under the title "*Opioid overdose* deaths can occur in patients with *naltrexone implants*" (our italics).

That leaves a single fatal opioid overdose in a patient who had an active implant, and in which the cause of death was acute narcotism, where the individual had injected heroin. Here at last is a case study that should be included, and the authors note that the effects of naltrexone can be overcome, and alert us to the danger of using excess heroin to overcome naltrexone blockade.

However, this information is less than new. *MIMS annual* notes under "Attempts to overcome [naltrexone] blockade":

> While ... [naltrexone] is a potent ... [opioid] antagonist ... the blockade produced ... is surmountable ... [and] poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenous opioids. Indeed, any attempt by a patient to overcome the antagonism by taking opioids is very dangerous and may lead to a fatal overdose ... Patients should be told of the serious consequences of trying to overcome the opiate blockade.[2]

It is also surprising that no denominator is attempted on the number of patients who may have received treatment by implanted naltrexone between 2000 and 2004. This information is available through the Therapeutic Goods Administration, and would have given the reader a clearer ability to evaluate the significance of this single case study. For example, one of the articles they cite reports one fatality in nearly 600 person-years of follow-up,[3] giving a very different impression of risk compared with the article by Gibson and colleagues.

Gary K Hulse, Professor of Addiction Medicine
Robert J Tait, Research Fellow
University of Western Australia, Perth, WA.
ghulse@meddent.uwa.edu.au

1 Gibson AE, Degenhardt LJ, Hall WD. Opioid overdose deaths can occur in patients with naltrexone implants. *Med J Aust* 2007; 186: 152-153.
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Moira G-B Sim

To the Editor: I read with interest the article by Gibson and colleagues,[1] who purport to have evaluated the claim that naltrexone "prevent[s] relapse to opioid use and therefore fatal opioid overdose". The article fails in its stated intent, as it neglects to provide adequate context and comparison in its evaluation of the five deaths between 2000 and 2004 identified through Australia's National Coroners Information System. The significance of the data cannot be assessed, as the authors omitted the number of naltrexone implants made available through the Therapeutic Goods Administration Special Access Scheme and comparison with other opioid users. This is extraordinary, given the high risk of death in this group both in and out of treatment.[2]

Of the five cases identified, three people no longer had active naltrexone implants and therefore could not be used to support the title "Opioid overdose deaths can occur in patients with naltrexone implants" any more than recurrence of depression can be attributed to previous antidepressant treatment. The remaining two deaths involved polydrug use, a known risk factor in overdoses;[3] naltrexone did not prevent death, but no clear causation was established.

In summary, this article was about two deaths among an unspecified number of naltrexone implant users across Australia over a period of 4–5 years, and it overlooked comparison with other opioid users, including those in the accepted gold-standard treatment, methadone maintenance. From the data presented, it is impossible to determine if the implant was associated with an increased or decreased risk of fatal overdose. A previously raised valid concern is the risk of overdose following all abstinence-based treatments.[4] Post-treatment outcomes from randomised controlled trials with naltrexone implants are needed to quantify this risk.

Despite the inadequacies described above, this article was published in a prestigious Australian medical journal, with a title linking opioid overdose with naltrexone, yet lacking the scientific basis for this association. Medical practitioners have limited time, frequently scan titles and abstracts, and rely on editors to provide summarised information based on scientific rigour.[5] Perhaps a more accurate title would have been "Two cases with naltrexone implants among X number of opioid-related deaths between 2000 and 2004".

Moira G-B Sim, Associate Professor and Chair, Independent Monitoring Committee, Naltrexone–Placebo Implant Trial
University of Western Australia, Perth, WA.
m.sim@ecu.edu.au

1 Gibson AE, Degenhardt LJ, Hall WH. Opioid overdose deaths can occur in patients with naltrexone implants. *Med J Aust* 2007; 186: 152-153.
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Colin L Brewer

TO THE EDITOR: As one of the first clinicians to use naltrexone implants (in 1997) and author of two references cited by Gibson et al,[1] I wish to comment on their article.

In writing that "Treatment with implanted naltrexone has been claimed to prevent . . . fatal opioid overdose", Gibson et al imply that this claim is untrue, or that anything less than total prevention is not useful. Lowest conventionally effective blood naltrexone levels (1–2 ng/mL) may indeed fail to block opioids, but such instances are extremely uncommon. (In any case, even after 100 mg of supervised oral naltrexone, trough naltrexone levels after 24 hours can be no higher than that.[2,3]) An article describing three cases of implant breakthrough is in preparation; 4.3 ng/mL was insufficient to prevent obvious opioid effects after one patient smoked about 80 mg of diamorphine equivalent.[4] The other cases involve much bigger opioid doses. However, higher naltrexone levels would almost certainly provide adequate blockade. Many patients test out the blockade soon after implantation[5] and while "pseudo-breakthrough" is occasionally seen,[2] true breakthrough with heroin or methadone is, I must stress, very rare.

Gibson et al cite my report that modest naltrexone levels can block 500 mg of pure diamorphine (an enormous dose).[3] They cite no reports of opioid receptor immunity to blockade by naltrexone. Therefore, unlike many drugs, naltrexone probably always does what it says on the packet. Accordingly, it follows that naltrexone implants can indeed prevent opioid overdose deaths, in the same sense that thyroxine prevents hypothyroidism. In all cases, adequate blood levels are important, and some patients, for various reasons, need more than average doses to achieve them. Gibson et al's article may be an argument for therapeutic drug monitoring or opioid challenge,[3,4] but not for therapeutic gloom.

Finally, details of all known coroner-linked "active" implant deaths in Western Australia have already been presented.[6] None appeared to be opioid-related; suicide, homicide, medical conditions and non-opioid overdoses caused them. Gibson et al report one apparently certain opioid overdose death despite an unprecedentedly high blood naltrexone level. This is puzzling, but postmortem opiate levels are notoriously misleading,[7,8] and the same may be true for naltrexone. Little is known about naltrexone disposition after death, perhaps because, unlike opioids, naltrexone is very rarely found in dead heroin addicts. In contrast, of the small proportion (27%) of patients actually completing a 28-day British inpatient opioid withdrawal program and thus losing their opioid tolerance, 10% died within a few months from resuming heroin.[9]

Colin L Brewer, Research Director
The Stapleford Centre, London, United Kingdom.
cbrewer@doctors.net.uk

1 Gibson AE, Degenhardt LJ, Hall WD. Opioid overdose deaths can occur in patients with naltrexone implants. *Med J Aust* 2007; 186: 152-153.
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Robert G Batey

TO THE EDITOR: Gibson and colleagues recently reported opioid overdose deaths occurring in patients with naltrexone implants.[1] The article is of great clinical significance, identifying that patients can override the effect of naltrexone and experience fatal opioid toxicity. However, it fails to address some important clinical and forensic issues that the five deaths highlight.

Firstly, it is disappointing that patients could be known to have been on naltrexone and not had naltrexone levels measured during the postmortem examination process. The absence of data compromises a full understanding of the circumstances leading to death.

In an "evidence-based medicine" society, it should no longer be acceptable that drug screening in coronial cases be restricted to drugs that have been measured for many years. Given the increasing use of a much wider range of drugs than has previously been the case, I suggest that all postmortem examinations on drug-using patients now include the measurement of naltrexone, if there is any history of naltrexone use, and buprenorphine, whether the patient is known to be on buprenorphine treatment or not. To this could be added the need to test for *para*-methoxyamphetamine and ecstasy.

The article also fails to comment on the level of clinical care provided to these patients. That a patient can be found to have, as well as naltrexone in their bloodstream, a variable combination of codeine, alprazolam, methamphetamine, propranolol, diazepam, amisulpride and morphine suggests that these patients were not necessarily being monitored or managed as well as they might have been.

This point is stressed because the role of naltrexone in the treatment of opioid dependence is often questioned based on a higher rate of death in patients on this drug compared with those on methadone or buprenorphine.[2] If used as recommended by national and state guidelines in a program of abstinence maintenance with appropriate monitoring, acceptable outcomes can be achieved.[3] Patients who use other drugs while on naltrexone are demonstrating a degree of instability requiring active clinical intervention. Perhaps the more important point this article raises is the need for close supervision and appropriate clinical response to instability, rather than the fact that heroin can override the effects of naltrexone at the opioid receptor.

Robert G Batey, Professor of Medicine
University of New South Wales, Sydney, NSW.
robert.batey@sswahs.nsw.gov.au

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Nikolaj Kunøe and Helge Waal

TO THE EDITOR: On the basis of five coroners' reports, Gibson et al warn of dangers connected to the use of naltrexone implants.[1] Two of the deaths occurred after the expected lifetime of the implant, a third after the implant had been removed, and a fourth was partially attributed to naltrexone by the coroner without detailing any physical evidence. Only the fifth case had the potential to support the authors' claims, with both a relatively high level of naltrexone and opioids present in the blood at the time of death. Still, as toxicological tests showed not only a high level of heroin, but also stimulants and benzodiazepines, the cause of death in this case is open to debate.

Some further comments seem appropriate. First, despite 30 years of scrutiny, systematic reviews find no support for claims of lethal side effects of naltrexone.[2] One coroner claiming otherwise in one death does not constitute evidence to the contrary, especially as no further physical evidence was presented. Second, any discontinuation of a lifesaving medication is followed by a period of increased vulnerability. This is a problem naltrexone treatment shares with all treatments for this group,[3] and indeed with most other medications designed to protect against premature death. In opioid addiction, patients die from overdose, and if their medication is discontinued, a larger proportion will do so. If prospective studies prove that opioid overdose can occur during naltrexone implant treatment, it would only be advisable to restrict the use of implants if the death rate proved higher than similar rates in maintenance treatment. Third, in the absence of high-quality evidence, authors will have to make logical arguments as to why they prefer one explanation over the alternatives. However, Gibson et al did neither, even though alternatives are readily available in the literature; for example, it is well known that sudden and unexpected death can occur as a consequence of the use of recreational doses of non-opioid drugs.[4]

We agree that great care needs to be taken to prevent overdose after the discontinuation of naltrexone medication, and agree that there is insufficient documentation to conclude on the safe lower limit for a protective naltrexone serum level. But to draw valid conclusions beyond that requires the direct and prospective observation of a large number of implant patients, or a review of such studies.

Nikolaj Kunøe, Psychologist and Research Fellow
Helge Waal, Professor, Senior Researcher and Director, Unit for Addiction Medicine
Department of Psychiatry, University of Oslo, Oslo, Norway.
nikolaj.kunoe@medisin.uio.no

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Eric Khong and Winston Choy

TO THE EDITOR: Gibson et al confidently conclude that the "clinical implications are clear: patients can die from an opioid overdose while undergoing naltrexone implant treatment".[1] The obvious implication from this statement and the general tone of the article encourages the reader to believe that naltrexone implants are somehow directly associated with opioid deaths.

However, more questions than answers are raised by the article. Five deaths were listed involving implantable naltrexone. Male 1 died of "acute narcotism", but do the authors believe this case demonstrates that the naltrexone implant used was implicated in the death? In the female case, the authors state that "Naltrexone was viewed by the coroner as playing a causal role in the death", but did the "numerous medications" and her "depression" also make a causal contribution to this death from a "combined drug effect"? The authors freely admit that the deaths of Males 3 and 4 "cannot be definitively linked to the naltrexone implant treatment" and their causes of death were "multiple drug toxicity", so why were these cases included? In addition, these men had their naltrexone implants removed 6 months previously. Male 2 had his naltrexone implant removed 2 weeks before his death. Of the five cases cited, it seems that only one actually died of an opioid overdose in the presence of a naltrexone implant.

Readers will agree with the authors that a risk of fatal opioid overdose exists in heroin or opioid users with and without treatment, regardless of the type of treatment chosen, and that medical professionals should provide balanced information to their patients. The community has strong feelings about the philosophy of treatments available for substance misuse. Therefore, as health professionals, it is important to ensure that what we write is not based upon personal beliefs and that facts are presented in an objective and independent manner. However, it seems that Gibson et al are providing, at best, poorly interpreted science and, at worst, speculation and alarmist rhetoric.

Eric Khong, Senior Lecturer[1]
Winston Choy, Senior Psychiatry Registrar[2]
1 School of Nursing, Midwifery and Postgraduate Medicine, Edith Cowan University, Perth, WA.
2 Community Forensic Mental Health Service, Perth, WA.
e.khong@ecu.edu.au

1 Gibson AE, Degenhardt LJ, Hall WH. Opioid overdose deaths can occur in patients with naltrexone implants. *Med J Aust* 2007; 186: 152-153. ❑

Amy E Gibson, Louisa J Degenhardt and Wayne D Hall

IN REPLY: We agree with Hulse and Tait, Brewer, Kunøe and Waal, and Sim that we need comparisons of mortality between naltrexone, other therapies such as methadone and buprenorphine, and heroin users outside of treatment. We have such a study in press.[1]

The point of our article was made simply in our title: opioid overdose deaths can occur during naltrexone implant treatment. This is important information because some doctors have advocated the coerced use of these implants on the unproven assumption that overdose deaths cannot occur in patients with these implants.[2,3] Our cases were obtained from the National Coroners Information System (NCIS), and Khong and Choy, and Hulse and Tait are correct: only two deaths occurred during naltrexone implant treatment. Cause of death was reported exactly as recorded by experienced professionals: the pathologist who conducted the autopsy in one case, and a pathologist and the coroner in the second case. Both deaths were attributed in part to naltrexone. We agree with Kunøe and Waal that care needs to be taken to avoid deaths occurring after naltrexone discontinuation: the three deaths out of treatment were included to highlight this period of increased risk after naltrexone implant cessation, as has been documented after cessation of oral naltrexone.[4]

Batey is correct when he points out the importance of good clinical care accompa-

nying naltrexone implant treatment. As naltrexone implants are not currently registered, we lack clinical guidelines regarding their use. Unfortunately, the NCIS does not routinely report clinical information, so we could not ascertain the level of psychosocial support being provided to the patients who died.

We agree with Sim, Batey, and Brewer that Australia needs therapeutic drug monitoring and studies of in-treatment and post-treatment mortality outcomes from randomised controlled trials of naltrexone implants. Indeed, in publishing these cases, it was our intention to highlight the need for such studies. We think it unacceptable that more than 1000 Australians have been given these implants[5] with little evidence of their safety and efficacy from randomised controlled trials or any systematic monitoring of their safety. Naltrexone has been implanted using special provisions under the Therapeutic Goods Administration on the grounds that the implants allegedly prevent fatal opioid overdoses. There is little evidence to support this claim, and the cases that we reported show that such deaths can occur. Scheduling of naltrexone, routine postmortem testing for naltrexone in suspected patients, and maintenance of national databases of naltrexone recipients would assist in investigating the full extent of the risks associated with naltrexone implant treatment.

Amy E Gibson, Senior Research Officer[1]
Louisa J Degenhardt, Associate Professor[1]
Wayne D Hall, Professor[2]
1 National Drug and Alcohol Research Centre, University of New South Wales, Sydney, NSW.
2 School of Population Health, University of Queensland, Brisbane, QLD.
amy.gibson@med.unsw.edu.au

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