Unplanned admissions to two Sydney public hospitals after naltrexone implants

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ABSTRACT

Objective: To describe hospital presentations related to the use of naltrexone implants, an unlicensed product used in Australia for treating heroin dependence.

Design: Retrospective case file audit.

Setting: Two Sydney teaching hospitals.

Patients: Identified through referrals to Drug and Alcohol Consultation–Liaison services over a 12-month period, August 2006 to July 2007.

Main outcome measures: Diagnosis, management and duration of admission.

Results: Twelve cases were identified: eight were definitely or probably related to naltrexone implants or the implantation procedure (rapid detoxification). Of these, six patients had severe opiate withdrawal and dehydration, with an average hospital stay of 2.3 days. One patient had an infection at the implant site, and one an underlying anxiety disorder requiring psychiatric admission. Three patients had analgesia complications, and one had unrelated cardiac arrhythmia.

Conclusions: These severe adverse events challenge the notion that naltrexone implants are a safe procedure and suggest a need for careful case selection and clinical management, and for closer regulatory monitoring to protect this marginalised and vulnerable population.

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Naltrexone is an opioid antagonist licensed internationally as an oral preparation for relapse prevention in treating heroin and alcohol dependence. However, its effectiveness for heroin dependence is compromised by poor treatment adherence and high relapse rates, with outcomes not significantly better than placebo for most patients.[1] This has led to the development of long-acting naltrexone products that seek to overcome problems of the patients' poor motivation and adherence to medication. A depot intramuscular injection product is licensed in the United States for treating alcohol dependence,[2-4] and a pilot study has reported favourable outcomes in opioid users.[5]

Several long-acting naltrexone implants have also been developed. The implant is inserted subcutaneously, typically in the abdominal wall, and releases therapeutic plasma levels of naltrexone for 3 to 6 months.[6] The treatment process usually commences with "rapid" detoxification from opiates, often using naloxone and sedation. Studies of several hundred individuals have been reported.[7-10] To date, no naltrexone implant has been approved for human use in Australia or internationally by regulatory bodies such as the Therapeutics Goods Administration (TGA).

Despite naltrexone implants being unlicensed, private clinics are delivering this treatment, and thousands of Australian cases have been reported.[11,12] One mechanism enabling the use of unlicensed products is the TGA Special Access Scheme for "persons who are seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment".[13] However, critics argue that naltrexone implants have not undergone the rigorous safety and efficacy licensing assessments required of medicinal products, and that this is of particular concern in view of their use in this vulnerable patient population.[14,15] Public facilities may be reluctant to deliver this intervention in the absence of a licensed therapeutic product and because of concerns about minimal safety and efficacy data and medicolegal indemnity.

A key issue in the debate is the extent to which naltrexone implants are associated with significant adverse events. The previously cited naltrexone implant studies reported no severe adverse events. In contrast, another study reported five deaths in patients treated with naltrexone implants: three after the proposed duration of the implant had expired, one non-opiate overdose, and one opiate overdose despite an "active" implant.[14] Another reported six severe adverse events: one case each of dehydration, seizure, pulmonary oedema, baclofen toxicity, benzodiazepine withdrawal, and death.[16] It has been argued that these complications were probably due to the detoxification procedure rather than the implant, and that such complications are not seen in Australia where the implant is usually preceded by safer rapid detoxification.[11,12] Nevertheless, it has been estimated that about 10% of the patients undergoing rapid detoxification and naltrexone implants at one clinic are referred to a local emergency department for assessment and management involving a "variable period of inpatient supportive care".[11]

Recently, a series of adverse events associated with naltrexone implants resulting in hospital admission has been encountered in two Sydney public hospitals that warrants reporting, given the paucity of published severe adverse events associated with the controversial and unregulated use of naltrexone implants.

METHODS

We report a case series of presentations to two teaching hospitals in Sydney associated with recent treatment with naltrexone implants. The series includes only patients referred to Drug and Alcohol Consultation–Liaison services at Liverpool Hospital (a 650-bed teaching hospital) and Royal Prince Alfred Hospital (a 700-bed tertiary care teaching hospital) over a 12-month period (August 2006 to July 2007), in which patients were noted to have recently had naltrexone implants inserted (within the preceding 6 months). This series does not necessarily reflect all implant-related presentations to the hospitals, as not all such patients may have been referred to the liaison services.

Hospital records were reviewed by an addiction medicine specialist, and key features of the presentation were deidentified

and extracted with a structured data instrument agreed to by the authors. Clinicians involved in the management of each patient reviewed and confirmed the details of each case summary. The project was approved as a quality assurance project of the Sydney South West Area Health Service Ethics Committee. One further case, of a patient with a panic attack immediately before the implant procedure, was found (not included).

RESULTS

Twelve patients were identified (Box).

Dehydration

Six of the 12 admissions were for severe dehydration and opiate withdrawal secondary to rapid opioid detoxification and naltrexone implant treatment. A similar clinical profile emerged: opiate withdrawal symptoms of severe vomiting and diarrhoea, abdominal cramps, agitation, lethargy and generalised aches started almost immediately after the procedure. Patients were unable to tolerate fluids or the oral symptomatic medications provided, and typically presented to the emergency department 1 or 2 days after the procedure (4 days in one case). On presentation, patients were usually in significant distress, with features of severe dehydration (eg, raised levels of urea and creatinine and electrolyte disturbances). Vomiting persisted, usually for days, despite a variety of parenteral anti-emetic agents (octreotide, ondansetron, metoclopramide). All patients required intravenous fluids and electrolyte stabilisation, and were admitted to hospital, staying a mean of 2.3 days (range 1–5, median 1.5) as inpatients (with two of the six patients discharging themselves against medical advice). Patients were also treated with a range of drugs for their symptoms, including hyoscine, benzodiazepines and clonidine. One patient was admitted to an intensive care unit with acute renal failure. Patients were discharged from hospital (generally as soon as they were tolerating fluids, but still complaining of mild to moderate withdrawal) a mean of 4.2 days (range 2–6, median 4) after the naltrexone implant.

Other adverse events

Several other severe adverse events were expected from our knowledge of naltrexone and the procedure. Six patients had a variety of reasons for admission. Patient 7 presented 10 weeks after implantation with an abscess at the implant site requiring surgical excision. Patient 8 had suicidal ideation and relapse of a pre-existing anxiety disorder within 1 week of the implant. This occurred at a time when the patient's regular psychiatrist was on leave, necessitating an admission to psychiatric emergency and crisis care. Patients 10, 11 and 12 had inadequate pain management after unrelated surgical procedures. The treating teams initially used opioid analgesics (morphine, fentanyl), with minimal effect. Effective analgesia was ultimately provided for Patient 10 with a ketamine infusion, oral tramadol and paracetamol.

Patient 9, who had a 2-week history of daily intravenous cocaine use, had an unexpected adverse event: cardiac arrhythmia (ventricular bigeminy) 24–48 hours after the detoxification and implant. She discharged herself against medical advice.

DISCUSSION

This case series identifies severe adverse events associated with the use of naltrexone implants, of particular relevance to staff in emergency departments, drug and alcohol services, pain management services, service providers engaged in delivering naltrexone implants, and regulatory agencies. These events challenge the notion that a naltrexone implant is a safe procedure, and indicate the need for careful case selection, careful clinical management and closer regulatory monitoring to protect this marginalised and vulnerable population.

Most of these cases (8/12) can be attributed to the naltrexone implant or implantation procedure. The case of Patient 8 was possibly implant-related, given the temporal sequence of events, and relapse of mental health conditions is a recognised complication of opiate withdrawal. The cardiac arrhythmia in Patient 9 was probably related to daily intravenous cocaine use.[17] Three further cases were unrelated to the naltrexone implant procedure, but reflect difficulties in providing these patients with pain relief. As previously reported,[18] non-opioid analgesia was effective where high opiate doses were not. However, a challenge for hospital staff is that patients reported that their implants had variable durations of action ranging from 3 to 12 months! Given that self-report is not always reliable, and that many patients presented after hours without referral and without reliable product information, it can be difficult to establish whether a naltrexone implant is still providing opioid blockade. Under such circumstances a trial of opioid analgesia (with close monitoring) may be warranted.

Clinical, regulatory and ethical implications arise from this case series. Patients should be warned of the associated risks, and appropriate procedures planned to respond to any complications. The emergence of severe psychiatric symptoms in one case highlights the importance of screening patients for underlying medical or psychiatric conditions, and importantly, coordinating with relevant service providers. Similarly, a close relationship between naltrexone implant providers and local emergency departments is important.[11] This was not evident in most of these cases, and it is concerning that the management of expected complications after this private treatment was "unexpectedly" transferred to the public health system.

Further, many of the adverse events may relate to the method of induction of naltrexone using rapid opiate detoxification rather than problems of the implant itself. In future, this may be avoided by delaying implant insertion until the patient can tolerate a single oral naltrexone challenge following standard (or rapid) opiate detoxification. Ultimately, uncoupling rapid detoxification from naltrexone implant treatment is not only required for regulatory and clinical assessment of safety, but would make any future treatment with naltrexone implants less expensive and more accessible to patients.

We are unable to estimate the incidence of severe adverse events associated with naltrexone implants. It is clear from discharge records that no consistent diagnosis-related group or International classification of diseases, 10th revision (ICD-10) code used for these admissions would enable such patients to be identified through an electronic search of hospital records. Furthermore, there was no documentation in the clinical notes that these cases had been reported to the TGA Adverse Drug Reaction Reporting System, suggesting an underreporting of implant-related adverse events. The presentation of at least 10 cases to one hospital in a 12-month period suggests that adverse events with naltrexone implants are not rare or uncommon.

Controlled trials are required to show the safety and efficacy of naltrexone implants. It may be appropriate to consider unlicensed treatments with a limited evidence base under special access schemes if a patient has a life-threatening condition and has not benefited from or cannot tolerate conventional treatment. It is not apparent how all of these cases met these criteria, as several

Patients attending emergency departments at two Sydney hospitals after naltrexone implants, August 2006 to July 2007

No.	Age (years) and sex	History and presentation	Diagnosis	Management
1	41 male	Heroin-dependent. ROD, NTX implant 17 Jan 2007. Attended ED 18 Jan 2007 with severe vomiting, not tolerating fluids, abdominal cramps, dehydrated.	Dehydration, opiate withdrawal secondary to NTX	IV fluids, ondansetron (12.5 mg bd IV, 4 days), metoclopramide (IV, 5 days), prochlorperazine (12.5 mg qid IV, 5 days), hyoscine (IV, 5 days), diazepam (5 days), haloperidol (1 mg daily IV, 5 days). Discharged 23 Jan 2007.
2	28 male	Heroin-dependent. ROD, NTX implant 31 Oct 2006. Attended ED 2 Nov 2006 with 3 days' severe vomiting, diarrhoea, not tolerating fluids, agitated.	Dehydration, opiate withdrawal secondary to NTX	IV fluids, ondansetron (4 mg IV x 1), hyoscine (IV), metoclopramide (10 mg IV x 2), diazepam. Discharged 3 Nov 2006. Withdrawal not abated, but patient tolerating fluids.
3	28 male	Heroin-dependent. ROD, NTX implant 20 Apr 2007. Severe vomiting and diarrhoea, not relieved by SC octreotide from local doctor. Attended ED 21 Apr 2007, not tolerating fluids.	Dehydration, opiate withdrawal secondary to NTX	IV fluids (4 days), metoclopramide (IV, 1 day), clonidine (0.15 mg qid, 4 days), diazepam (1 day), pantoprazole (40 mg daily). Discharged 26 Apr 2007, tolerating fluids.
4	23 male	Heroin-dependent. ROD, NTX implant 2 May 2007. Attended ED 6 May 2007 with persistent vomiting, diarrhoea, not tolerating fluids, poor sleep.	Dehydration, opiate withdrawal secondary to NTX	IV fluids, ondansetron (4 mg IV x 1), hyoscine (20 mg IV x 1). Tolerating oral fluids. Discharged himself against medical advice 6 May 2007.
5	21 female	Brief history of heroin use. ROD, NTX implant 26 Jun 2007. Attended ED 28 Jun 2007 with vomiting, diarrhoea, not tolerating fluids. Urea clearance 26 mL/min, creatinine clearance 470 mL/min, blood pressure 65/30 mmHg, pulse 160 beats/min.	Acute renal failure, metabolic acidosis secondary to severe opiate withdrawal	Admitted ICU. IV fluids, electrolyte stabilisation. Discharged herself against medical advice 30 Jun 2007 (still vomiting).
6	22 female	Heroin-dependent. ROD, NTX implant 29 Nov 2006. Dry retching not responding to octreotide (0.1 mg, SC), hyoscine (20 mg IM) from local doctor. Attended ED 30 Nov 2006 with vomiting, diarrhoea, not tolerating fluids.	Dehydration, opiate withdrawal secondary to NTX	IV fluids, ondansetron (4 mg IV qid), hyoscine, metoclopramide, diazepam. Moderate to severe withdrawal. Tolerating fluids. Discharged 1 Dec 2006.
7	25 male	Heroin-dependent. 5 prior NTX implants. Attended ED 4 Mar 2007 with 5 days' pain, inflammation, pus at implant site. Spreading cellulitis. Stated that "3 month" NTX implant had been inserted ~10 weeks earlier.	Localised abscess at implant site	IV fluids, flucloxacillin (1 g qid, IV), benzylpenicillin (1.2 g qid, IV). Drainage of abscess 6 Mar 2007. Tramadol (100 mg qid), diclofenac (50 mg tds), paracetamol for pain. Discharged 7 Mar 2007.
8	30 male	Multiple-substance user with no prior specific treatment. History of drug-induced psychosis and post-traumatic stress disorder. ROD, NTX implant 7 Jul 2007. Presented 13 Jul 2007 with anxiety, paranoia, suicidal ideation.	Anxiety disorder	Admitted to psychiatric emergency and crisis care. Olanzapine 5–10 mg as required. Discharged 16 Jul 2007.
9	24 female	3 years' methadone treatment. No heroin but daily IV cocaine use. ROD, NTX implant 25 Oct 2006. Referred to ED by local doctor 27 Oct 2006 with dizziness, tachypnoea (32), bradycardia (33). Afebrile.	Severe cardiac arrhythmia	Observation and monitoring in ED. Ventricular bigeminy. Patient discharged herself against medical advice on 27 Oct 2006 before further investigations or management.
10	37 female	Presented 5 Jul 2007 with right upper lobe pneumonia and empyema. Stated that "12 month" NTX implant had been inserted Feb 2007. Implant became infected Apr 2007 and was partially excised.	Necrotising pneumonia, empyema (unrelated to implant)	Fentanyl infusion (up to 20 μg/h, IV), patient-controlled ketamine (up to 5 mg/h, SC), tramadol (200 mg bd), ibuprofen (400 mg bd) for analgesia. Oral oxycodone had no effect and was ceased. Patient discharged weeks later.
11	26 male	Attended ED 4 Oct 2006 after a fall with pain in right hip. Stated that "3 month" NTX implant had been inserted 10 weeks earlier. Recent clonazepam, cannabis, amphetamine use.	Posterior dislocation right hip	Morphine 22.5 mg (over 4 h, IV) to little effect. Closed reduction right hip under anaesthesia. Discharged 6 Oct 2006.
12	23 male	Motor vehicle accident and shooting. Admitted 17 Apr 2007. NTX implant inserted 4 months before (duration of action not documented).	Fractured left femur	Initial analgesia with ketamine (40 mg, IV) and femoral nerve block. Patient-controlled morphine (10 mg/h) after surgery had no effect and was ceased. Tramadol (100 mg bd), non-steroidal anti-inflammatory drugs, paracetamol until discharge 21 Apr 2007.

ROD = rapid opioid detoxification. NTX = naltrexone. ED = emergency department. IV = intravenous. SC = subcutaneous. IM = intramuscular. bd = twice a day. tds = three times a day. qid = four times a day. ICU = intensive care unit.

Unless otherwise stated, drugs given orally as follows: metoclopramide (10 mg qid), hyoscine (20 mg 6–8 hourly), diazepam (5–10 mg qid), paracetamol (1 g qid). ◆

patients reported no previous alcohol and drug specialist treatment, and others were actively enrolled in effective methadone programs. The widespread and unregulated use of naltrexone implants without appropriate safeguards for patients, their families and service providers should be restricted until this therapeutic product has been assessed for safety and effectiveness.

COMPETING INTERESTS

None identified.

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