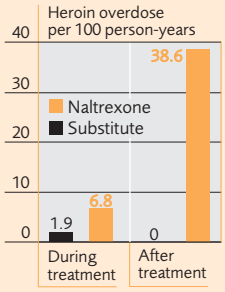
11.1 Opiate antagonist treatment risks overdose

Findings The most comprehensive recent study of serious medical incidents during and after treatment for opioid dependence has highlighted the risk of overdose and death when patients stop taking opiate-blocking ('antagonist') drugs. In contrast, substitute prescribing was relatively safe even after the patient had left treatment.

The data comes from 12 trials in Australia's national evaluation of drug-based treatments for opioid dependence. These involved 1244 patients of whom 324 started long-term treatment with the opiate antagonist naltrexone and 920 with an opiate substitute (methadone, LAAM, or buprenorphine). Naltrexone is typically used to help patients remain opiate-free after detoxification.

Patients' records were monitored for up to six months. While they remained in treatment none died, and though there were fewer non-fatal heroin overdoses on methadone, the differences were not statistically significant. After patients left treatment the death rate significantly increased. Only after naltrexone treatment was this (three deaths) due to heroin overdose. Heroin overdose overall (fatal and non-fatal) also increased significantly after stopping naltrexone, when there were 24 incidents. There were none after ending substitute prescribing; assuming for statistical purposes one incident still left the heroin overdose rate nearly eight times greater after stopping naltrexone, a statistically significant difference. Nearly half the post-naltrexone overdoses occurred within the first two weeks.



In context The study confirms the high risk of overdose and death associated with opiate antagonist treatment and the relative safety of methadone maintenance. Based on these figures, on average in the six months after stopping treatment 100 ex-naltrexone patients can expect to experience nearly 20 heroin overdoses from which two or three will die, while neither would occur after ending substitute prescribing. The study's major limitation is that patients were not randomly allocated to the different types of treatment, leaving open the possibility that pre-existing risk factors caused the findings.

The methadone-naltrexone risk differential arises in two ways. First, if it is successful, naltrexone treatment (and any other abstinence-based regime) means the patient loses their tolerance to opiate-type drugs, increasing the risk of overdose if the patient leaves treatment and resumes heroin use. Second, compared to the same period after starting methadone, many more people run this risk by dropping out of treatment and resuming heroin use.

Naltrexone drop-out is concentrated in the induction phase. Sheltered detoxification and naltrexone initiation regimes (inpatient and/or under sedation or anaesthesia) mean that a high proportion of patients complete withdrawal, lose tolerance and start naltrexone treatment, but also that more later relapse. By increasing the post-withdrawal relapse rate, these regimes may place more ex-patients at risk of overdose than outpatient procedures, whose high 'failure' rate leaves many patients with a degree of protective tolerance.

However, the naltrexone relapse rate can be reduced, most importantly by recruiting an effective treatment partner from close family or friends to supervise and encourage naltrexone consumption. This has been particularly effective where family ties are strong and young addicts still live in the family home. It may be accompanied by family therapy to manage the tensions and deal with any family dysfunction underlying the addiction. Any bona-fide supportive therapy may also improve short-term retention on naltrexone, but the evidence (in particular for a persisting effect) is strongest for therapies such as community reinforcement and behavioural couples therapy which involve treatment partners, and specifically aim to help them monitor and reinforce naltrexone consumption. The better the patient-partner(s) relationships, the greater the commitment of the family, and the more complete the supervision, the better the results, but when these are questionable, or other prognostic factors are poor, retention can still be disappointing.

Rewards and sanctions built into the patient's non-domestic life also improve compliance and outcomes. Groups such as professionals, business people, and offenders, with much to lose from relapsing and for whom methadone maintenance is less of an option, are most likely to do well on naltrexone.

Material rewards (usually vouchers for goods and services) tied to taking naltrexone or to drug-free urine tests also improve retention and reduce drug use, but only while the regime is operating and less effectively than strong family involvement.

Practice implications Reducing drug-related deaths is a national target in England. Related guidance recognises the heightened overdose risk after detoxification, says this should not be forced on patients in substitute prescribing, and argues for post-withdrawal support to reduce the risk ◤ Additional reading. The Australian government has produced naltrexone treatment guidelines (download from www.health.gov.au) which stress (and ask treatment staff to stress to patients) the overdose risk. To reduce this they advise that treatment is limited to heroin users demonstrably committed to long-term abstinence, that patients are reviewed at first weekly, and that alternative approaches are considered for those who relapse, especially repeatedly.

Most likely to succeed on naltrexone are patients with a close and positive relationship with live-in relatives or partners who can be drawn on (and supported through family and allied therapies) to monitor and reward naltrexone consumption. Patients facing legal, professional or occupational sanctions if they resume opiate use also do well. In general, the greater the patient's social capital (job, family) and psychological stability, and the less severe and entrenched their opiate problem, the more likely they are to benefit from treatment. When these elements are missing, patients may be encouraged to comply through material rewards, but the longer term prognosis is poor unless time bought this way can be used create incentives and sanctions built in to their family and working lives. Where the prognosis is poor, attempting detoxification with or without naltrexone to follow heightens the risk of overdose and death, and substitute prescribing or intensive rehabilitation should be considered instead.

LINKS
Nuggets 11.2 10.3 7.1 2.1
Nuggette p. 9 issue 9 • *Overdosing on opiates*, issues 4 and 5

Featured studies Digiusto E. *et al*. "Serious adverse events in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD)." *Addiction*: 2004, 99, p. 450–460. DS.

Additional reading ❶ *Reducing drug-related deaths. Guidance for drug treatment providers* ❷ *Commissioning services to reduce drug-related deaths.* Both National Treatment Agency, 2003. Copies www.nta.nhs.uk.

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