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▶ Ultra-rapid opiate detoxification followed by nine months of naltrexone maintenance therapy in Iran.

Naderi-Heiden A., Naderi A., Naderi M.M. et al.

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Further evidence from Iran that rapid withdrawal from opioids under anaesthesia followed by the opioid-blocking drug naltrexone can work for highly motivated caseloads with copious 'recovery capital'. For others this expensive and when not adequately controlled, potentially risky procedure generally ends in overdose-threatening relapse.

Summary Ultra-rapid opiate detoxification typically involves a day or two of hospitalisation during which patients dependent on opiate-type ('opioid') drugs like heroin are anaesthetised or deeply sedated while the opiate-blocking drug naloxone is administered by infusion in to the blood stream to precipitate sudden withdrawal. Then patients are started on prescriptions of naltrexone tablets which (as long as they are taken) continue to block the effects of opiate-type drugs, an attempt to prevent the relapse to regular opioid use which commonly follows withdrawal.

For the featured study records were analysed of 45 male patients admitted for such procedures between 2003 and 2005 to a surgical centre's department of anaesthesiology in Iran's capital Tehran. They were selected to be free of dependence on other drugs or alcohol except for cannabis, and free of severe physical or mental illness which might contraindicate general anaesthesia. For this and for other reasons they were relatively well placed to overcome their dependence via an abstinence-oriented route. Forty of the 45 were addicted to opium and just five injected. On average in their early 30s, they were committed to abstinence and had good family support. Over half were married and nearly 80% employed. They were attending an expensive private hospital so came predominantly from wealthy families, who (in the absence of a public welfare support

system) can exert considerable pressure on opiate-dependent relatives, as can wives for whom such dependence is grounds for divorce. Also, in Iran familial solidarity is highly developed and can provide a high level of support and motivation for abstinence-oriented patients.

On admission patients were detoxified by means of a six-hour infusion of naloxone under general anaesthesia; medications used were midazolam, propofol, clonidine and the muscle relaxant atracurium. For 24 hours after patients woke staff documented severity of withdrawal on a standard checklist of physical signs such as runny noses, sweating, cramps and dilated pupils.

Usually discharge was scheduled for the day after detoxification. Then naltrexone (50mg/day) was prescribed for nine months with assessments every four weeks by a clinician with extensive experience in the treatment of dependence. At these consultations, naltrexone was re-prescribed and the patient's progress monitored, verified with the patients' agreement by talking to their families. For the purposes of the study, patients who missed these visits were considered relapsed.

Main findings

All the patients were successfully detoxified during inpatient stays of two days (one night) for all but two, who stayed three days. Withdrawal signs after awakening peaked within one to three hours but were generally few and mild, consisting universally of dilated pupils plus typically one other symptom. Severe symptoms were observed only in two patients, one an injector and the other dependent on cannabis as well as opioids. There were no serious adverse events, but there was one case of prolonged unconsciousness, eight of mild and transient confusion, and six of depressed mood. Monitored cardiopulmonary signs were stable during the whole treatment in all patients.

Of the 45, 36 (80%) continued naltrexone therapy and reported relapse-free status for the entire nine-month observation period.

The authors' conclusions

The primary purpose of opiate detoxification under general anaesthesia is to achieve a complete but quick and painless physical withdrawal. In this it generally succeeded. Patients typically exhibited only mild signs of withdrawal and required just one night in hospital, as reported by other studies. Propofol provides an excellent means of controlling excessive arousal of body systems caused by withdrawal, while clonidine allows for large doses of opioid antagonists to be delivered without significant changes in heart rate or blood pressure. The method used in the present study appears to be safe when performed by experienced anaesthetists and with round-the-clock care from qualified nursing staff for at least 24 hours.

Though this detoxification method ensures the initiation of long-term naltrexone treatment, its continuation might not depend on how the patient was withdrawn, but factors like ancillary drug use, family stability, and employment. The featured study's sample enjoyed relatively good personal and occupational situations and the close family support typical in Iran. Generally they did not inject, and were to a large extent free of official or legal pressure; voluntary detoxification is a positive prognostic feature in abstinence-oriented therapy. These factors might explain why 80% continued naltrexone

treatment for at least nine months, though retention on naltrexone does not always mean abstinence from opiate-type drugs.

Such results contrast with those of an Australian study, in which few patients completed nine months of naltrexone treatment after rapid withdrawal. In this study patients injected heroin and sometimes also abused alcohol, cannabis and benzodiazepines. [Editor's note: also half were unemployed, around 80% single, and generally they were poorly educated.]

Naltrexone significantly reduces relapse apparently only when rigorously supervised. New long-acting injectable or implantable formulations may address this limitation. But the featured study shows that in Iran, with patients generally not dependent on other drugs and with strong family as well as continuous medical support, oral naltrexone following rapid withdrawal can be sustained by most for many months.

Together with other studies, these findings suggest that not only the individual but also cultural and economic factors should be taken in to consideration. In Europe and North America rapid detoxification and naltrexone are not first-line detoxification treatments, not just because patients differ, but perhaps also because the health-care systems in those countries generally provide for the expensive option of inpatient detoxification over several days or weeks while doses of opiate-type drugs are gradually reduced to zero.

FINDINGS The authors of the featured study are appropriately cautious about generalising their findings beyond Iran and the type of patients they sampled, and the absence of a control group offered no treatment or an alternative means the results cannot securely be attributed to the studied treatment. However, with on average nearly ten years of opiate use behind them and still relatively young, it seems unlikely that the 80% completion and abstinence rate reported by the study would have happened anyway without treatment. Another gap is what happened to the patients after treatment ended and they were no longer shielded by naltrexone which their families probably ensured they took.

Relevance to other countries

An obvious difference from Britain and many other countries is the dominance of non-injecting routes of administration in Iran, but in recent years British drug users have also moved to non-injecting routes, an estimated 137,000 injectors in England in 2004/05 falling to 117,000 in 2006/07. Estimates for England in 2009/10 were that of the 306,150 opiate and/or crack users, just a third were injectors. These population trends fed in to the drug treatment system. By 2011/2012, just 18% of drug users starting treatment in England were recorded as currently injecting and over half – 55% – had never injected; in 2004–2005, the figures were 30% and 49% respectively. In Scotland the proportion of patients starting drug treatment who had injected in the previous month fell from 28% in 2006/07 to 24% in 2010/11 and by more still in younger age groups with presumably shorter drug using careers. In particular, smoking or 'chasing' (inhaling fumes) opiates – generally heroin rather than opium – has long been established in Britain.

Notwithstanding national and caseload differences, the study reinforces indications that even in countries such as Britain and the USA, similar types of patients in similar circumstances can do well on oral naltrexone. The role of rapid withdrawal is to ensure

they at least start the procedure. Such patients include those committed to abstinence because considerable leverage is exerted over them by families, employers, professional bodies, or the criminal justice system, and can be exerted because the patients have much to lose (freedom, well paid jobs, reputations, careers, families, homes) by not complying. They also have the support and stability to be able to respond to that pressure by remaining in treatment and avoiding lasting relapse to opiate-type drugs.

Opiate blockers or substitutes?

For other types of patients, the majority in countries like Britain, rather than drugs which block opiates, the prescription of opiate-type drugs like methadone remains the mainstay of opiate addiction treatment (1 2). British guidelines relegate naltrexone to the minority of patients highly motivated to remain in an abstinence programme, contrasted with the more widespread applicability and more securely established effectiveness of substitute prescribing using methadone or buprenorphine. They also emphasise the need for anti-relapse support after detoxification. More promising but not without their complications and controversies are long-acting forms of naltrexone placed under the skin as implants or injected. These have yet to be licensed for medical use in the UK, but some forms have been elsewhere.

The only study to have randomly allocated patients detoxified as inpatients to continuing treatment with oral naltrexone or with an opiate-type drug (buprenorphine) was terminated early when it became apparent that buprenorphine was clearly the best option. Supplementing counselling with naltrexone only slightly and non-significantly improved treatment retention and heroin use outcomes compared to a placebo. In contrast, outcomes were clearly and universally superior for the buprenorphine patients, significantly better than placebo, and generally also significantly better than naltrexone. Conducted in Malaysia, typically the patients were poorly educated single men with a history of imprisonment who had been using heroin for on average 15 years and had used near-daily in the previous month – a much less promising caseload than in Iran, adding weight to the proposition that such patients usually do better on drugs like buprenorphine and methadone.

Safety concerns

Among caseloads not endowed with substantial resources and on whom leverage is weak or ineffective, rapid relapse is the norm even after they have been able to complete detoxification; oral opiate blocking medication does little to improve the situation. Relapse brings with it what in some circumstances is a very high risk of death due to opiate overdose, because patients coming off naltrexone have entirely lost their tolerance to opiate-type drugs; the doses they used to take all too often prove fatal. Such concerns are less salient when opioids are taken by the much safer and controllable inhalation route.

It seems that with modern-day anaesthetic techniques and high quality care, rapid withdrawal procedures can be very safe. Nevertheless, due to safety concerns, British guidelines say the more radical of these procedures entailing (as in the featured study) anaesthesia or deep sedation "must not be offered", as in milder terms did guidelines published by the World Health Organization, though these did see a non-routine role for

procedures entailing *minimal* sedation. Similarly, a review for the Cochrane collaboration found that lighter forms of sedation ameliorate the severity of the withdrawal experience about as well as deep sedation or anaesthesia and are less risky. With no countervailing benefits but greater risk, the reviewers counselled against the more radical procedures.

For further discussion of these issues see this Findings hot topic on naltrexone implants and rapid detoxification, and earlier Findings analysis whose background notes (1 2) reviewed rapid withdrawal evidence to date. Other key sources are these Cochrane reviews on oral naltrexone and rapid withdrawal under heavy sedation or anaesthesia. For all relevant Findings analyses run these searches on naltrexone treatment for opiate addiction and on rapid withdrawal from opiate-type drugs.

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