Nugget 7.1

Ultra-rapid techniques guarantee completion of opiate detoxification; abstinence depends on what follows

Findings A study commissioned by the Israeli Ministry of Health has compared outcomes from the world's largest private provider of 'ultra-rapid' opiate detoxification with those from a conventional, publicly funded 30-day inpatient regime.[1] While more patients completed the rapid detoxification procedure, fewer remained abstinent.

At the private clinic withdrawal is precipitated by opiate antagonists (drugs which blocks the effects of opiates) while the patient is deeply sedated. Normally just one night's stay is required. Before discharge the patient starts daily naltrexone administration intended to continue for a year to prevent relapse.

60% of 139 'rapid' patients and 92% of 87 'conventional' patients who had been treated 12 to 18 months earlier were interviewed by phone. All the 'rapid' patients had completed detoxification compared to 81% in the conventional programme, but nearly twice as many 'conventional' patients had remained abstinent from heroin – 42% versus 22%. The gap remained significant when differences between the groups were taken into account. None of the measured variables (including number of prior detoxification attempts) indicated that certain patients were suited to one of the programmes rather than the other. Even if the rapid programme had been implemented as a public service it would have cost nearly twice as much as the conventional programme per abstinent client.

In context Though details are scant, the study seems to be an example of how the benefits of rapid detoxification under sedation or anaesthesia (virtually guaranteed completion) can be undermined without adequate continuing support – the key factor in good long-term outcomes regardless of the detoxification method.

In terms of short-term outcomes, how rapid detoxification compares with conventional programmes will depend on the quality of the respective treatments. In the featured study, the completion rate in the conventional programme suggests

that (on this indicator) quality was far higher than in typical British detoxification centres. In contrast, long-term outcomes from the rapid detoxification clinic, though not atypical, have been bettered.

Deep sedation or anaesthesia entail a small risk of serious complications including death. Assuming alternatives procedures are available and of acceptable quality, relatively few people will need (as opposed to choose) to undergo procedures requiring intensive care. Equally rapid procedures using lighter sedation (but sufficient to induce sleep) are likely to be safer and may have wider application. Regimes during which withdrawal is precipitated but patients remain fully conscious take a day or two longer, do not guarantee completion and involve greater discomfort, but can produce good completion rates for inpatients and good long-term outcomes.

Costs of rapid detoxification under deep sedation or anaesthesia are comparable to conventional inpatient detoxification and since completion rates are higher, the cost per completed detoxification is lower. However, there is some (limited) evidence that, given the same post-detoxification support, long-term outcomes are similar. This implies that the cost per long-term remission too will be similar. Using lighter sedation eliminates the need for intensive care, potentially making it more cost-effective.

As with any antagonist-based treatment, loss of tolerance creates a serious risk of fatal overdose if discharged patients stop taking their medication and return to heroin use.

Practice implications Detoxification under anaesthesia or deep sedation may have a role for patients who are good candidates for continuing relapse prevention therapy (the minority), and among these only patients who have not completed or will not countenance withdrawal using less radical procedures. In this sense the method's main public health benefit could be that it extends the opportunity to become opiate-free to a wider range of people.

How big this number might be depends on the quality and attractiveness of the alternatives. Poor retention at British inpatient detoxification units creates scope for a technique where retention is not an issue. Similarly, the lack of these facilities in some areas and waiting lists in others create a gap which could be filled by a high throughput method such as rapid detoxification, especially if lighter sedation methods prove acceptable and effective. However, high throughput could simply mean frequently repeated detoxifications and added danger of overdose due to loss of tolerance unless accompanied by effective post-detoxification relapse prevention.

Fears that rapid and relatively painless detoxification would reduce engagement with longer term therapy, or hopes that it might provide a more auspicious start to an opiate-free life, do not seem to have been realised. Long-term recovery depends less on the detoxification technology than on what follows, particularly whether a supervisor is on hand (such as a family member or spouse) to help ensure naltrexone is taken and on the quality and intensity of continuing monitoring and therapeutic support. It is too early to judge whether naltrexone implants will safely and effectively reduce the need for supervision and support.

Patients should be warned that though they will be shielded from the worst of the withdrawal process many will feel unwell for days or weeks after discharge, the process is not an entirely painless exit from dependence.

Featured studies Lawental E. "Ultra rapid opiate detoxification as compared to 30-day inpatient detoxification program – a retrospective follow-up study." *Journal of Substance Abuse*: 2000, 11(2), p. 173–181. Copies: apply DrugScope.

Additional reading O'Connor P.G., *et al*. "Rapid and ultra-rapid opioid detoxification techniques." *Journal of the American Medical Association*: 1998, 279(3), p. 229–234. Copies: apply DrugScope.

Contacts Eli Lawental, Haifa Drug Abuse Treatment Centre, Rambam Medical Center, 26 Hagefen Street, Haifa, Israel, e-mail lawental@netvision.net.il.

Links *Nuggets* **5.5 1.6**.

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Appendix. Notes for Nugget 7.1

These notes are not for publication but may be made available on request. They are not intended to be a systematic and comprehensive review of the literature. The intention is to collect sufficient information to support the published *In context* and *Practice implications* text.

The featured study

It is unclear whether the 22% and 42% outcome rates refer to continuous abstinence since treatment[2] or abstinence at the time of follow up[3] and whether only heroin[4] is being referred to or all illegal drugs plus alcohol.[5]"Self reported current heroin use" – p. 176.[6] It is also unclear whether all the proportions reported in the outcomes table refer to all the people interviewed or to relevant sub-sets, eg, whether the 90+% who resumed heroin use is a proportion of those who did not remain abstinent from all drugs or of the full follow-up sample. Telephone follow up interviews may be less reliable when not backed up be physical tests for drug use.

On the measured variables the patient groups were surprisingly similar in drug use history, current criminal status and major demographic variables and about the same proportions were in work at follow up. The only significant difference at intake was the greater number of recent arrests of those in conventional detoxification. Just 27% of the rapid group and 16% of the conventional detoxification group[7] had been accepted for and completed their conscripted service in the Israeli army; failure to complete army service is considered an indicator of relatively intractable disability and/or social marginality.[8]

However, the conventional regime was a public programme whilst the rapid option was a costly private treatment, and patients entered treatment in the normal way rather than by random allocation. Unmeasured differences between the personal characteristics and the social and economic resources of clients in the two programmes might have affected outcomes. Though some of these potential differences seem likely to have resulted in a better prognosis for the private patients (eg, less criminality, perhaps greater material resources), it is also conceivable that only addicts highly motivated towards abstinence would be prepared to undergo and largely stick with the 30 day regime, while those less prepared to undergo discomfort and inconvenience in order to achieve this goal would opt for a two-day procedure which promises a painless leap to abstinence.

The rapid treatment programme incorporated aftercare using naltrexone to prevent relapse but how well this was implemented (a 'supervisor' to ensure the drug is taken is considered an important factor in the treatment's success) is unknown. The clinic's literature emphasises the neuronal impact of the rapid procedure and of the naltrexone which follows rather than aftercare, rehabilitation or psychosocial therapy.[9]"We differ from other Rapid Detox methods due to the fact of the fast recovery and the effective receptor blockage. Our patients feel psychologically better and craving is no longer an issue."

"We do not believe in addictive personalities."

"We do not believe that opiate dependent men or women have weak personalities."

“We do not believe in long term psychotherapies for formerly opiate dependent patients.”

“We do not believe that after treatment patients should perceive themselves as still being an ‘addict’.”

“Opiate Dependency requires the appropriate medical care. Unfortunately, this central nervous system disorder has been attempted to be treated by social workers, psychologists, psychiatrists, and law enforcement personnel. However, times have changed, and Opiate Dependency has finally been recognized as a central nervous system disorder caused by continuous opiate intake.” A 30-day scheduled stay at the health service facility(ies) suggests these were not just detoxification centres but also at least initiated rehabilitation. The fact that over eight in ten patients were retained long enough to complete their detoxification indicates a programme towards the top end on this variable[10] and one whose retention is probably far better than the average in England.[11] There is no information about the aftercare available following detoxification at the conventional centre(s) or whether the centre(s) in the study were typical of those in Israel. Conceivably the scope and quality of the inpatient programme(s), the aftercare resources available through the network of public services, and the de-emphasis on psychosocial support in the particular rapid programme studied, account for the difference in post-detoxification abstinence. Similar aftercare approaches and resources might have eliminated the gap.

Generally, subjects most difficult to locate in follow up studies tend to be the ones who had the worst prognoses and the worst outcomes.[12] [13] [14] If this was the case in the featured study the abstinence rate advantage of the conventional programme would have been even greater.[15] However, differences in the availability and/or validity of the information used to locate patients (in the case of rapid patients this was the telephone number provided by the private facility) or in their willingness to be located (anonymity is a selling point for the private facility) could instead account for the difference in follow-up rates.

Rapid detoxification methods

Normally withdrawal from opiate drugs results in withdrawal symptoms which peak after two to three days and fade after about a week. Detoxification procedures ameliorate this discomfort by administering gradually reducing doses of a substitute drug such as methadone or by using drugs such as lofexidine and clonidine which reduce some of the physical symptoms. With prior stabilisation and post-detoxification observation, the procedure typically requires a hospital stay of two or three weeks. In contrast, opiate antagonist drugs such as naltrexone and naloxone result in immediate and severe withdrawal symptoms.[16] Normally these would be unacceptable, but methods have been developed to shield patients from these symptoms, enabling them to rapidly complete detoxification and cutting hospital stays and detoxification periods to days rather than weeks. One method (sometimes termed rapid opiate detoxification) uses clonidine or lofexidine and other drugs before, during after naltrexone to control physical withdrawal symptoms.[17] Variants on this procedure have used benzodiazepine sedation to ease and shorten the process.[18] [19] Withdrawal takes place over two or three days and medication may continue to be required for another two or three days.[20]

However, whilst the patient is conscious the rapidity with which withdrawal can be induced is limited by the capacity of the available drugs to counter the severity of the symptoms.[21] [22] Clonidine does ameliorate the symptoms and with large doses of benzodiazepine sedatives most patients can transfer to naltrexone and be discharged within a day. Even with this combination of drugs, severe restlessness during precipitated withdrawal is common and some degree of withdrawal discomfort remains.[23] Severe restlessness plus profuse diarrhoea and vomiting present a nursing problem and a hazard to patient and staff.[24]

What are sometimes termed 'ultra-rapid methods also precipitate withdrawal using naltrexone or naloxone. The most severe withdrawal phase is compressed to just hours[25] and the whole process to a day or two[26] whilst conscious discomfort is avoided by anaesthetising the patient or deeply sedating them during the worst of the withdrawal period. This is emerging technology and many variants have been tried with no standard or optimal regime yet apparent.[27] Current methods typically use naltrexone (though often naloxone[28]) to precipitate withdrawal, a short-acting anaesthetic such as propofol to see the patient through the few hours of withdrawal without unnecessarily prolonging unconsciousness and to minimise hangover effects,[29] and to control withdrawal symptoms clonidine and benzodiazepines plus drugs to counter sickness and diarrhoea. Midazolam may be used to induce deep sedation rather than anaesthesia.[30] Unlike less radical procedures, most forms of 'ultra-rapid' detoxification require intensive inpatient care. However, newer variants use benzodiazepines to induce a lighter sedation from which patients can be roused but which is sufficient to control discomfort and prevent the worst of the experience being remembered.[31] [32]

The aim (not always achieved) is that on discharge patients are free from the most troubling withdrawal symptoms and no longer need heroin or a substitute drug in order to prevent their recurrence.[33] Usually the treatment plan envisages an immediate transfer to continuing doses of the opiate blocking drug naltrexone to prevent relapse to regular heroin use. Since naltrexone can be initiated while the patient is in hospital, not only can completion of detoxification itself be virtually guaranteed but so can at least the start of relapse prevention pharmacotherapy.

Ultra-rapid detoxification: the issues

Once a patient enters the ultra-rapid procedure completion is virtually guaranteed as they are in no condition to abscond.[34] Though this seems a major advantage over outpatient detoxification methods, a more appropriate comparator for ultra-rapid detoxification is specialist inpatient detoxification. In Britain, probably the majority of inpatients complete the withdrawal phase[35] though completion of the entire regime is much lower[36] and internationally averages just under 60% for regimes of up to 21 days.[37]

If rapid treatments and inpatient regimes are considered as alternatives, there are at least two major issues in terms of drug use outcomes. The first is whether higher withdrawal completion rates in rapid regimes translate into a greater proportion of treatment starters maintaining abstinence or avoiding relapse to dependent use. This could occur even if the same proportions of treatment *completers* maintain positive outcomes. The second issue is whether the regimes give patients who complete them a better or worse platform on which to build lasting recovery. Inpatient

detoxification usually involves two weeks or more in hospital during which time the patient is consciously undergoing withdrawal and interacting with therapeutic staff and other patients undergoing the same procedure. This provides an opportunity to plan for the future in a safely contained environment without the complications of intoxication or the temptations of life outside the ward and to at least start to build a platform for an addiction-free life on discharge. Alternatively, the rapid and often unconscious transition to drug-free status (a 'clean start') afforded by ultra-rapid methods may result in better long-term outcomes.[38] In either type of treatment, if patients resume opiate use after detoxification the treatment may not just have failed to act as a precursor to tackling addiction but will also have increased the risk of death through overdose due to loss of tolerance.[39] [40] [41] [42] [43] Inevitably much will depend not on the detoxification technology used but on whether the opportunities afforded by an inpatient stay are taken and on the preparation and follow up either side of the detoxification episode.

If rapid and conventional treatments are considered not as alternatives but as possibly appropriate for different patients, the issue becomes how to identify such patients. Both types of consideration will be influenced by cost and safety. Though each day of the intensive care required for most forms of ultra-rapid detoxification is more expensive than a day on an inpatient detoxification ward, the fact that just one or two days day are required could mean costs are comparable.[44] Deep sedation or anaesthesia add a small element of risk to what is otherwise an inherently benign procedure but may be justified if this means people are freed of the highly dangerous lifestyle usually entailed in addiction to illicitly obtained opiates who would not be freed by other methods. Among these may be people who might manage a conventional detoxification but who for family or occupational reasons (or perhaps purely for comfort or convenience) prefer a swifter exit from physical dependence.[45] As with other forms of medicine, this demand is more likely to be met by privately rather than publicly funded care.

Reviews of the effectiveness of ultra-rapid detoxification

Several recent comprehensive reviews are available and are largely relied on here for their assessment of the evidence and their expert judgements on the balance of risks and benefits. Only major studies with some degree of post-treatment follow-up are separately analysed, focusing on those not able to be included in the O'Connor and Kosten review published in 1998, the standard reference document.

It is important to remember that many ultra-rapid detoxification studies have involved privately provided and very expensive treatments paid for by the patient or their family and pre-selection for motivated patients most likely to succeed. Both factors can be expected to increase retention in treatment and improve outcomes.[46] Even if standard demographic indicators suggest patient groups are comparable, they may not be in terms of social and economic resources, psychological preparedness for detoxification and investment in achieving an opiate-free life. Conceivably the same intake procedures applied to conventional approaches might improve both retention and longer term outcomes. An early study[47] and several recent studies have involved patients at publicly funded services.[48] However, some are as yet unpublished[49] [50] and others employed exclusion criteria which made the sample to a degree atypical of publicly funded treatment samples in Britain

particularly in terms of stability, closeness with family, and dependence on drugs other than opiates.[51] [52] [53] [54]

In 1997 Colin Brewer, one of the most experienced British practitioners of rapid and ultra-rapid detoxification, gave a detailed account of the treatments which have been tried and of the potential complications of rapid and intensified withdrawal.[55] Among these are severe diarrhoea, vomiting, anxiety and insomnia and pains, particularly in the lower back and legs. There is at least a theoretical risk that the drug used to reverse deep sedation in ultra-rapid detoxification using midazolam could precipitate seizures in patients also dependent on benzodiazepines. Patients normally emerge from ultra-rapid detoxification without the full range of severe symptoms which would be expected at the same time after abrupt withdrawal of opiates but these and other symptoms may still be present. Two deaths known to the author after anaesthesia-assisted ultra-rapid detoxification may have been due to inadequate care and two more may have been linked to cocaine use in the hours after discharge (possibly reflecting a failure to examine the patients thoroughly enough – they were both day patients – to establish their likely behaviour on release and to take steps to counter any risks).[56] Another death has been seen after ultra-rapid detoxification using heavy sedation instead of anaesthesia. Since Dr Brewer's review one of the deaths (which occurred in Britain) has resulted in an anaesthetist being struck off the medical register. Quality of care was poor in a number of respects. Undiagnosed brain damage previously sustained by the patient[57] may have been the complicating factor which with the anaesthesia or other elements of the treatment led to seizure and death.[58] Dr Brewer admits that it cannot be claimed that ultra-rapid detoxification produces better long-term results than conventional methods but argues that it is justified for patients who are motivated to stop using opiates[59] but who will not countenance, would fail, or have repeatedly failed to complete conventional detoxifications. The added risk is acknowledged but it is argued that in a young patient group not subject at the same time to surgery these are small and that if these are explained to patients they (as with other potentially risky medical procedures) have a right to choose whether to run those risks. Dr Brewer argues that people regularly risk highly improbable but possible injury or death for the sake of comfort and/or speed, and that (especially if they pay for themselves) opiate addicts are no different. Studies are cited suggesting that long-term abstinence from opiates after the procedure is dependent on the selection of motivated patients who can be returned to close supervision of continued antagonist therapy by their families. Without this, rapid return to opiate use can be the norm.

From Dr Brewer's account it seems clear that the potential for complications to occur and the need for pharmacological and medical procedures to be instigated routinely or as needed to counter these complications makes ultra-rapid detoxification a highly complex procedure in comparison with gradual methadone reduction. With experience, skilled staff and up to date knowledge many problems can be dealt with, but the converse is that the potential for sub-standard practice to result in risk to health and unplanned patient discomfort is greater than in conventional procedures. Relatively light sedation methods avoid these problems to the point where they can be conducted at the patient's home but the major study of this technique has yet to be published.[60]

An important US review of the literature on rapid and ultra-rapid opiate detoxification by O'Connor and Kosten published in 1998 found that just three studies had followed up patients after ultra-rapid detoxification (in two cases for just a month) and that the evidence was insufficient for any conclusion to be reached on the relative efficacy of accelerated versus conventional procedures.[61] The conclusion was that expense and the risks entailed in anaesthesia and deep sedation mean that ultra-rapid procedures are unlikely to be offered routinely but may have a role for those who have not completed or will not countenance withdrawal using conventional methods or who for family or social reasons (eg, employment) wish to restrict their time in hospital.

The same year a review of the evidence for the Australian government reached similar conclusions, arguing that ultra-rapid detoxification might have a place only for small number of addicts so sensitive to withdrawal symptoms that they are unwilling to withdraw using conventional methods.[62] A later Australian review involving one of the same authors concluded that ultra-rapid detoxification does compress the detoxification procedure and has a high completion rate.[63] However, it was argued, in this respect it is not unique. Other forms of antagonist-accelerated detoxification which take slightly longer but entail only light sedation ands during which patients remain conscious also do the same at lower cost and without the risks of general anaesthesia. Neither, it was argued, is there any evidence that rapid procedures improve longer term abstinence outcomes. Since "all but a handful of patients can withdraw without anaesthesia" it queried whether even the very small risks were worth running and whether intensive care beds, specialist nursing staff and anaesthetists might not be better deployed in treating conditions for which these resources are essential.

Also in 1998 an editorial in *Addiction* from an eminent US addiction specialist who developed some of the rapid detoxification procedures acknowledged that ultra-rapid detoxification might have a place for addicts particularly fearful of withdrawal who would welcome getting the worst of it over while unconscious and for those who have not completed withdrawal using other methods.[64] However, the author concluded that the risk/benefit ratio for ultra-rapid detoxification was currently skewed to the risk side largely due insufficient data on adverse consequences on health and on long-term outcomes.

UK addiction treatment guidelines published in 1999 cautioned that naltrexone-precipitated withdrawal should be carried out only by specialists with inpatient facilities and that the effectiveness and safety of ultra-rapid methods using anaesthetics and opiate antagonists had yet to be established.[65]

The same year researchers and clinicians from the National Addiction Centre in England reviewed the evidence and concluded that it was insufficient for an assessment of whether ultra-rapid detoxification under anaesthesia was warranted given that it introduced an element of risk to opiate withdrawal which in itself is not a risk to health.[66] In so far as it helped people become free of heroin addiction it would reduce the considerable risks of this lifestyle, but alternative detoxification procedures are available which do not entail anaesthesia. The authors accepted that anaesthesia in healthy patients is a low risk procedure but pointed out that opiate dependent patients are commonly also dependent on other drugs and commonly suffer physical complaints which create added complications and risks. In particular,

safety and effectiveness had yet to be established in opioid addicts who are also dependent on other drugs such as benzodiazepines, stimulants and alcohol, subjects typically excluded from the better studies. They cite the example of the patient in Britain with history of severe injury who died during the procedure after suffering a seizure, and point out that seizures are more likely in patients who are effectively also being withdrawn from alcohol or benzodiazepines and/or who have a history of head injuries. A similar point has been made by O'Connor and Kosten, authors of the 1998 US review, who advised that clinicians considering ultra-rapid detoxification should carefully examine the patient for other illnesses including HIV infection and cocaine abuse.[67] The risks of anaesthesia among patients intoxicated with cocaine is well known to anaesthetists but the evidence for any extra risk due to HIV infection is contested.[68]

In April 2000 a review conducted under the Cochrane procedure found no adequately controlled studies comparing treatment regimes involving the administration of opioid antagonists under sedation or anaesthesia with other approaches to detoxification, and only very limited information on referral to ongoing treatment and relapse to opioid use.[69] It was therefore impossible to draw any conclusions about the long-term effectiveness or cost-effectiveness of ultra-rapid procedures. The approach must, it was concluded, be regarded as experimental with both risks and benefits remaining uncertain. The authors cautioned that the risk of vomiting during sedation and of respiratory depression should limit the approach to facilities equipped for intubation and assisted ventilation and with the capacity to respond to adverse events.

While reportedly physical withdrawal symptoms are mild when the patient awakes from anaesthesia or sedation,[70] it is less clear that these or subjective symptoms of withdrawal remain in abeyance after discharge. In a review of opioid withdrawal methods in general (also published in 2000), the authors of the Cochrane review have pointed out that the lack of investigations into the severity of withdrawal after discharge mean there is no solid evidence that the ultra-rapid procedure does compress withdrawal into a few hours, and that some reports have noted that symptoms lasted for several days.[71] Similar points have been made by other authors.[72] [73] The review also cited studies reporting that some procedures led to severe withdrawal symptoms such as vomiting and diarrhoea in a majority of patients and other symptoms including respiratory depression and renal dysfunction in a minority.

Selected studies included in the O'Connor review

One of the follow-up studies cited in the O'Connor review was from Spain. It is separately considered here because it involved 300 patients, by far the largest sample of the studies reviewed.[74] To be included in the study patients had to have experienced unsuccessful previous detoxifications (on average four) but to have evidenced high motivation in a selection interview. Patients could choose either accelerated inpatient detoxification using clonidine and naltrexone or ultra-rapid detoxification under sedation. Those who chose the latter were randomised either to a deep sedation or to lighter but still quite deep sedation,[75] both induced in an intensive care ward. In both procedures nearly all the patients were discharged after just 24 hours in hospital and on average they stayed just 10 hours. Withdrawal symptoms were largely suppressed and were not significantly more severe in the

lighter sedation group; all the patients completed the procedure. In 13 cases complications occurred during the procedure. Depressed breathing due to excessive sedation was the most frequent and required intervention more often in those more deeply sedated (four out of 150 patients) and in heroin smokers. One deeply sedated patient developed pneumonia which resolved after 10 days' treatment including five days in hospital. Another seven patients had to be kept in hospital for up to two days due to vomiting, diarrhoea or fever. Patients were discharged under the supervision of a relative and were prescribed naltrexone for a year. For the first month they were visited by a doctor and a psychologist at first daily, who took urine tests. During this period self-reports and the tests revealed that just 7% had relapsed to heroin use or used cocaine. Though each day of care in the unit was expensive, the fact that just one day was required meant that the procedure cost less than half the cost of 10-day inpatient detoxification. Patients were recruited over an 18-month period, suggesting that despite the intake criteria there was reasonable demand for the service. The main question marks are over longer term outcomes and over whether the previous failures of the patients were failures to complete detoxification (in which case the 100% completion rate in the rapid procedure is an advance on previous performance) or a failure to maintain abstinence following completed detoxification (in which case the key factor in the better outcomes may not have been rapid detoxification but intensive aftercare).

Another of the follow-up studies cited in the O'Connor review was conducted in Israel.[76] It is separately considered here because a later paper not available to the review provides further data.[77] 120 men were randomly selected out of 640 who had been withdrawn from opiates under anaesthesia. The treatment package included immediate transfer to naltrexone maintenance to be continued for to six to nine months supported by 15 counselling sessions. In less than about 10% of cases patients had to be retained in hospital another day to treat complaints including severe diarrhoea, vomiting, anxiety, aggression or exhaustion. They had all been accompanied to the intake interview by a 'significant other' who was usually a family member. One to two years after their detoxification, 83 patients were interviewed over the phone and their responses corroborated by a family member or an alternative significant other.[78] 57% had not relapsed (relapse was defined as daily opiate use for at least two weeks) and 40% had not used opiates at all. Relapse was strongly related to a history of imprisonment and unemployment in the year before treatment and to unemployment and associating with other addicts after treatment. The treatment was provided on a private basis so patients may not have been comparable (if only in the resources available to them via their families or other sources) to the publicly treated patients who normally feature in follow-up studies. However, almost 80% had been arrested and over half imprisoned, and they had each on average undertaken nearly three previous detoxifications. Most relapses began within the first two months and relapse was strongly associated with not taking naltrexone during this period.

Later studies not included in the O'Connor review

A 1999 Australian study trialed ultra-rapid inpatient detoxification using naltrexone and clonidine, but under benzodiazepine sedation[79] seemingly lighter than that assessed in the 'light' sedation condition in the large Spanish trial.[80] 30 patients, half withdrawing from methadone and half from heroin, stayed in a general medical

ward usually for one or (if symptoms warranted – 11 out of 15 heroin withdrawers needed just one night) two or three nights. When withdrawal peaked after naltrexone administration patients woke and evidenced moderate distress and almost all became confused to the point of delirium, but nursing care was straightforward. The ensuing stay in hospital seems to have been a rather miserable experience characterised by depression, feeling washed out, loss of appetite and vomiting (better controlled by octreotide than ondansetron). Looking back on the experience, most patients rated it severe but acceptable. Retention on naltrexone was 80% at day eight but fell to 17% at three months. However, at this time 11 of the 30 patients (including some who had terminated naltrexone) were either abstinent or only using heroin occasionally. Loss of tolerance posed a risk of overdose for patients who stopped or took a break from naltrexone and resumed heroin use. One died and two had to be revived using naloxone. The study shows that a set of addicts seemingly typical of these seen at British services who are motivated to withdraw from opioids can do so quickly in a general ward without need for a high level of nursing care, and that despite the unpleasantness (from the acute phase, only vaguely recalled) many prefer this to more drawn out procedures. Each patient had a case manager and were seen daily for the first four days and then weekly at a community clinic, not a high level of support. Neither were they selected for high levels of social support, yet about a third maintained near abstinence for at least three months.

A Swiss study involved 20 patients detoxifying generally after relatively low dose methadone maintenance, though seven were using heroin daily in large amounts.[81] All had been through previous detoxifications. Half the applicants for the treatment had been refused because assessed as lacking sufficient motivation. Rather than being anaesthetised, patients were sedated to sleep on midazolam though were rousable and occasionally woke during the procedure. Despite medication (which may not have been given in high enough doses[82] or was not effective – to control vomiting ondansetron was used[83]), two out of three vomited and three out of four had diarrhoea lasting for the whole day. An example of what can go wrong was one patient who entered full withdrawal only after she woke, presumably because the naltrexone tablet had not been swallowed down and was dislodged when she moved. Except for patients who had planned to stay for other reasons, discharge was 36 hours after admission with a prescription/recommendation for naltrexone to be supervised by the patient's doctors (all experienced in addictions) or by the clinic. Naltrexone intake was not systematically supervised and no set therapeutic regime was followed. Contact with the patients' therapists or doctors and if necessary the patients themselves was used to assess relapse status in the six months after detoxification. 80% returned to some level of heroin use at some time during the six months following their discharge, most within the first month. Some had been able to recover and resume naltrexone therapy. 60% of all the patients had resumed daily heroin use or entered methadone maintenance. The authors believe the high relapse rate may have been due to insufficient supervision of post-detoxification naltrexone administration.

A study at two US centres found that all 123 detoxifications under anaesthesia during the periods studied were completed and all the patients transferred to naltrexone.[84] At one of the sites a traditional 14-day methadone reduction programme had been completed by just 42% of patients. 14 of the procedures were followed by serious medical incidents including gastrointestinal complaints,

persistent vomiting, a transient psychotic episode and delirium tremens in a patient who had not revealed his co-dependence on alcohol. Six months later 90% of the patients were recontacted of whom 55% (representing about half of the full sample) had avoided re-addiction to opioid drugs. About 39% had not used opioids at all. To be included in the programme patients had to have a supportive associate to aid compliance with the treatment, and the programme included a range of long-term aftercare options. When it occurred, relapse tended to be within the first four weeks after treatment. A price of $75000 for the treatment might mean the patients in this study were not typical of opiate addicted patients in either the USA or the UK.

In a German psychiatric hospital 108 methadone patients were withdrawn from opiates by antagonist precipitated withdrawal under anaesthesia over an average inpatient stay of about 6 days.[85] Two-thirds were successfully followed up. In the first month after discharge half complained of feeling unwell. Though three-quarters would recommend the procedure to others 38% would not themselves repeat the experience. Only 30% took naltrexone after discharge and six months later just a third were abstinent from heroin cocaine and amphetamines.

In Israel small samples of patients referrred for opiate detoxification by a social services department were interviewed by phone about 13 months after detoxification. Those who requested rapid detoxification under aneasthesia were also immediately started on a nine month naltrexone regime. The remainder received a conventional 30-day inpatient detoxification using clonidine but were not then offered naltrexone. However, they did use significantly more outpatient aftercare services, attending over 21 times during the 13 month follow up compared to 11 for the naltrexone patients. At follow up there was no significant difference in the number who had returned to regular heroin use (on naltrexone, 38%; conventional detox, 31%) or to any heroin use.[86]

Though the authors are based in the Netherlands the reference to Great Britain in a short report in the *Journal of the American Medical Association* suggests the work was done in the UK.[87] 30 patients were consecutively referred either to rapid detoxification with naltrexone under general anesthesia followed by long-term naltrexone use or substitution with methadone followed by gradual tapering of the methadone dose and long-term naltrexone. After giving informed consent, the first 15 eligible patients were assigned to rapid detoxification and the next 15 to traditional methadone treatment. Patients were mainly unemployed men with a long history of heroin addiction who had undergone many previous treeatments. All patients were followed up for 3 months and drug use was assessed urine tests. All 15 patients in the rapid detoxification group completed the 7-day rapid detoxification programme, but only 8 completed methadone tapering. During the follow-up period, 5 patients dropped out of the rapid detoxification arm, and 3 of the remaining 8 patients dropped out of the methadone group. Thus, the authors say, rapid detoxification led to a 3-month abstinence rate of 67% vs 33% in the methadone group, not statistically significant. However, this conclusion equates dropping out of treatment with heroin use and remaining in it with abstinence; neither assumption may be correct. The average 3-month intent-to-treat cost for rapid detoxification was $5850 vs $4230 in the methadone group. The average cost per treatment success was $8775 in the rapid detoxification group vs $12685 in the methadone group.

A study from Spain recorded immediate outcomes among 1368 patients assessed at one of two detoxification clinics, one private, one public. They were then detoxified at home under relatively light sedation (using midazolam) under the supervision of a family member who maintained close phone contact with the medical team.[88] The procedure is similar to that trialed in Australia on a general medical ward without a high level of nursing care.[89] Typically patients were rousable and could walk with assistance but were confused and restless for 4–6 hours after taking naltrexone. Vomiting and diarrhoea were the most common withdrawal effects (each experience by under 15% of patients) and by 24 hours symptoms were moderate. Carers felt unable to manage 24 patients who were taken to hospital; none required more than a brief admission for rehydration. All but three patients returned to the clinic the next day for a further dose of naltrexone. Though advised not take heroin for at least 12 hours before the procedure, failure to do so was not a contraindication for proceeding. During the same period 3500 patients had opted instead for conventional inpatient detoxification. Including the patients reported on above, over 3000 patients have been treated using this procedure with, the authors report, no significant complications. The authors have since replaced loperamide (blocked by naltrexone) with octreotide to control vomiting and diarrhoea. Octreotide must be injected giving a greater role for medical staff, but has also been administered by trained family members.

Unpublished studies

In Australia heroin or methadone dependent patients were randomly allocated to induction on to naltrexone after inpatient detoxification either under anaesthesia (47 patients) or under sedation (70 patients).[90] The procedures averaged 1–2 days. Outcomes were compared with induction on to naltrexone after conventional inpatient or outpatient detoxification; allocation to these treatments does not seem to have been random. All procedures were carried out by the public health system. The rapid techniques achieved near 100% transfer to naltrexone compared to 37% and 17% respectively for the conventional procedures and over 80% of patients were satisfied enough with the experience to say they would definitely repeat or recommend it. Across all the groups, 12 months later about 60% of patients were not dependent on opiates. The detoxification procedure made no difference to long-term outcomes, which instead were greatly influenced by the availability of effective abstinence maintenance programmes. Four overdose deaths occurred among patients who had relapsed to heroin use, in each case at least 14 days after their last dose of naltrexone. For each successful induction on to naltrexone the rapid techniques cost around a third of the conventional programmes. However, since drug use outcomes were similar, the cost per patient who did not relapse to heroin addiction may have favoured the conventional outpatient regime.[91] The authors argued that anaesthesia should be discontinued because it was riskier but no more effective than sedation, that sedation-assisted detoxification was a cost-effective means of induction on to naltrexone, and that it should be conducted in a centre where alternative treatments are available and within a specialised inpatient setting which retains and monitors patients for at least 24 hours after induction on to naltrexone. They saw a particular role for rapid detoxification among methadone maintenance patients who wish to move towards abstinence.

In Australia high rates of completion of detoxification under anaesthesia and sedation were followed by disappointing six-month retention on naltrexone in a national study of opiate pharmacotherapies yet to be reported in detail.[92]

In the same country 101 heroin addicts were randomised to withdrawal under anaesthesia or withdrawal using standard inpatient procedures (including clonidine and other symptom relief as needed) before transferring to nine months of naltrexone maintenance.[93] To enter the study patients had to be aiming for abstinence, prepared to undergo either procedure, and to have a suitable adult to support them whilst on naltrexone. Nearly half the patients were unemployed; just 6% were in full time work. Three out of 37 patients given octreotide experienced vomiting and diarrhoea compared to seven of the 11 not given it. 40 of the 51 patients rapidly withdrawn started naltrexone but just 14 of the 50 withdrawn conventionally, an advantage which translated into slightly more (but still very few) days on which naltrexone was taken over the follow-up period. However, the advantages gained by rapid detoxification and induction lasted only three months. By six months very few patients from either group were still taking naltrexone and half were known to be using heroin. Including patients who could not be re-interviewed, up to 74% of the rapid group and 88% of the conventional group may have relapsed to heroin use. Hair analyses indicated that the rapid group had used less heroin over the six-month follow up. At the six-month point there was only a non-significant trend towards fewer rapid detoxification participants self-reporting heroin use. The authors observed that the costs of the two procedures were comparable and that the rapid procedure helped maximise initial transfer to naltrexone but did little to improve retention or heroin use outcomes in the medium term.

Naltrexone implants in conjunction with rapid detoxification.

Rapid detoxification is often thought most appropriate for patients unable to complete conventional detoxification because it eliminates the need for 'will power' to complete the process. Such patients may be considered suitable for a relapse prevention technology which also removes the need for willpower by implanting naltrexone whilst patients are still under sedation or anaesthesia. The potential for the two processes to be combined has been recognised in the UK[94] and in Australia.[95]

In Germany 108 opiate addicts were detoxified under anaesthesia as inpatients and transferred to naltrexone; for 69 this was in the form of implants, for the remainder oral.[96] They had all failed several previous detoxification attempts. Though all lived in stable conditions, 43% were neither in education nor employed. One month later 81% remained abstinent from opiates, at six months 61% out of the 93 traced were abstinent(about 53% of the starting sample), and at a year 53% of the 90 traced (about 44% of the starting sample). Nearly two-thirds of the patients had monthly implants of naltrexone. 20% more implants patients maintained abstinence during the period they could be followed up than patients taking naltrexone orally.

In the USA emergency department physicians have documented six cases of serious complications after one-day outpatient detoxification under anaesthesia in conjunction with an implant of naltrexone.[97] The respective contributions of the detoxification procedure and the implant to the complications could not be disentangled. Typically, severe withdrawal symptoms had persisted after discharge. Two of the patients died, one in the aftermath of the rapid detoxification, the other

due to a heroin overdose. This occurred two weeks after discharge from the treatment of her complications (at which time the naltrexone implant was removed) when she had stopped taking oral naltrexone. Nationally records were found of another nine patients who had died after a similar procedure between April 1998 and July 2001 and a further one in whom the implantation had occurred a month after rapid detoxification. All six cases had been treated at a single clinic run by a doctor against whom on 1 October 1999 the New Jersey State Attorney General's office filed a complaint charging that his treatment was dangerous and was not followed up with proper outpatient care.[98] [99] In some of the six cases and in most of the recorded deaths patients were typically discharged without intensive medical care into the custody of parents or other associates or sometimes alone.

Results have been presented from for the first 55 patients in Britain to be implanted subcutaneously with naltrexone during rapid detoxification under general anaesthesia or sedation (or in one case after outpatient withdrawal).[100] Half were unemployed. 12 weeks later information was obtained on all the patients by phone or in person either directly or via families and other people close to them. Though most had 'tested' the naltrexone antagonism during the first week, just 11 had relapsed to opiate use including two who had entered methadone maintenance. Two had died, one from suicide and the other from reasons apparently unrelated to the implant. Four patients developed infection at the implant site. All responded to antibiotics. Eight developed painless sterile abscesses which resolved without antibiotics or incision.

Good implant technology is vital both to avoid adverse events and to maintain a steady and adequate flow of the drug over an appropriate period. From the published literature it appears that this technology has not yet stabilised.[101] [102]

Does ultra-rapid detoxification really compress the withdrawal period?

The most relevant study of whether rapid detoxification really does compress the withdrawal period compared to conventional procedures comes from the Austrian team which first developed ultra-rapid detoxification under anaesthesia. Depending on which detoxification procedure was to follow (patients were not randomly allocated), before detoxification patients were stabilised on either methadone or morphine sufficient to suppress withdrawal symptoms and ratings were taken of subjective and objective symptoms. The morphine patients then underwent rapid detoxification under anaesthesia and stayed in hospital for four days; methadone patients had their methadone reduced to zero over about 20 days. Measures of opiate withdrawal were re-taken two days after the patients' urine tests confirmed they were opiate free. Both groups were back to their low pre-detoxification levels of withdrawal symptoms and there was no significant difference between them. However, this point had been reached in six days by the rapid detoxification group and in three weeks by the conventional group. Four of the 29 patients in the conventional group left before treatment could be completed, none in the rapid group.[103]

In China withdrawal symptoms in ultra-rapid patients 24 hours after anaesthesia were compared to patients five days after admission to a 10-day methadone reduction programme. Craving, anxiety and sleep disturbance were better in the

ultra-rapid patients but diarrhoea was worse and aches, nausea and vomiting scores were not statistically different.[104]

In a Swiss study of 20 patients detoxifying via sedation on midazolam, withdrawal symptoms peaked at about one hour but remained elevated throughout the 24 hours when measures were taken and most patients continued to complain of at least moderate symptoms for three to five days including anorexia, nausea, vomiting, abdominal cramps and anxiety and depression.[105] The possibility that this represented resurgence of methadone withdrawal after the initial naltrexone doses had worn off was discounted because withdrawal symptoms also persisted among patients known to have continued on naltrexone. One possible explanation for the relatively long withdrawal period is that propofol was not used. This is known to shorten the withdrawal period relative to another anaesthetic and may do the same with respect to midazolam sedation.[106]

Such protracted symptoms are at odds with other reports such as the large Spanish study using midazolam and propofol sedation rather than anaesthesia.[107] In this study withdrawal symptoms resurfaced when patients woke from sedation and a substantial minority experienced profuse sweating, diarrhoea and vomiting. It is unclear how long these lasted though it is known that just 2.3% of patients had to remain in hospital for a short period because of the severity of these or other symptoms. By a measure which does not include diarrhoea and vomiting, at 16 hours withdrawal symptoms were minimal and remained so to at least 24 hours.

Outcomes from alternative rapid methods

The O'Connor review found two rapid detoxification studies which reported post-detoxification outcomes after precipitated withdrawal during which patients remained conscious.[108] In one, 9 out of 17 patients remained on naltrexone treatment for a month and in the other 125 from 152 had not dropped out from naltrexone treatment by three months. Only particularly significant studies included in the O'Connor review or later studies not included are separately analysed here.

Reviews conducted under the Cochrane procedure in 2000 and 2001 have investigated the evidence for precipitating withdrawal using opioid antagonists (generally naltrexone) and managing the symptoms with adrenergic agonists such as clonidine.[109] [110] Most studies were of procedures carried out on an outpatient basis but with extended medical care on the first day of treatment. The severity of withdrawal among patients on naltrexone and clonidine combination was reported to be at least equivalent to withdrawal managed by clonidine alone, and probably more severe in the first few days of treatment. The naltrexone-clonidine combination can result in good rates of completion of withdrawal (75%–95%) but one study reported an extremely low completion rate (7%). The most common side effects were vomiting, diarrhoea and delirium (in one study affecting most subjects) lasting several hours following administration of the first dose of naltrexone. In a review of opioid withdrawal methods in general (also published in 2000), the authors of the Cochrane reviews said completion rates were generally around 90% but that side effects including delirium (not typical of normal opiate withdrawal) necessitated a high level of medical care.[111]

Only one study included in the O'Connor review used double blind random allocation to different detoxification methods, the accepted standard for

pharmacotherapy trials. 162 US primary care clinic outpatients were allocated either to unaccelerated withdrawal ameliorated by clonidine, naltrexone-accelerated withdrawal plus clonidine, or to buprenorphine (which can precipitate withdrawal in opiate addicted subjects, has opiate-type effects, and has a relatively mild withdrawal profile) plus clonidine.[112] Neither patients nor staff knew which drugs they were taking.[113] Over eight days patients were visited daily (except days 6 and 7) by primary care staff. All were transferred to naltrexone to maintain abstinence reaching a full dose in eight (clonidine only), three (naltrexone-accelerated) and five (buprenorphine) days. In the two quicker procedures over 80% of patients reached this point but just 65% on clonidine alone. However, by day eight treatment retention was similar in both groups in the range 54–65%, but tended to be worst after naltrexone acceleration. Withdrawal severity was lowest on buprenorphine, a finding also reported by other studies comparing buprenorphine and clonidine.[114 115] Patients do not seem to have paid for their treatments; about 20% were employed. Heroin use in the month before treatment averaged about a 'bag' a week. perhaps raising doubts over how dependent they were on entering treatment. Doubts are reinforced by the fact that withdrawal severity never rose much over intake levels and that, though the buprenorphine condition provided only low doses (3mg) of the drug and no clonidine, in the first three days withdrawal severity fell slightly. Blinding robbed staff of the chance to prepare patients for what to expect, perhaps a factor in drop out.

A later study administered a single high dose (32mg) of sublingual buprenorphine to addicted heroin smokers.[116] To avoid buprenorphine-precipitated withdrawal, they were asked to abstain from heroin for a day; probably as a result, all patients admitted to the treatment (nine out of ten) were showing signs of withdrawal. The procedure was conducted on a day patient basis in a hospital to which patients returned for monitoring for the next six days. The buprenorphine rapidly resolved withdrawal symptoms to minimal levels within an hour and symptoms remained low throughout the study with some restlessness on days three and four when the buprenorphine (in high doses the opiate substitution effects last several days) can be expected to have worn off. All nine subjects completed the trial and the absence of withdrawal symptoms when opiate antagonist therapy commenced on day seven suggests that they had remained abstinent from heroin. Eight continued to remain abstinent over the next six months. Patients were not in typical circumstances. Most were police informers housed in 'safe houses' visited twice daily by police. Detoxification was part of the package offered by police, perhaps as a way out of a heroin scene which for them held particular dangers. All had 'caretakers' to accompany them to the hospital and presumably to help them through the following days and months. Whilst these circumstances may have affected retention and abstinence rates there is no reason to believe they would have affected the level of withdrawal symptoms.

At the Bethlem Hospital's inpatient addiction unit in England, patients stabilised on methadone for three days have been detoxified on an accelerated five-day lofexidine regime which started at high doses; the more usual protocol builds up to full doses and is completed in 10 days.[117] A comparison between these two regimes and a 10-day methadone taper showed that withdrawal symptoms remitted faster (to intake levels by about eight days) on the 5-day regime. In each group about 80% of patients completed detoxification after hospital stays averaging about 20 days. Later the same

team took accelerated lofexidine detoxification a step further by inducing withdrawal with naltrexone building to a full opiate-blocking dose of naltrexone on day four when lofexidine was discontinued.[118] Compared to a seven day lofexidine detoxification in this study and with the regimes in the previous study, withdrawal symptoms remitted far more quickly reaching a low level by day four only approached by days eight to nine in the unaccelerated lofexidine regimes. 82% in the accelerated condition completed detoxification, significantly more than in the comparator condition (73%) and lengths of stay averaged 15 days. Though in both studies lengths of stay were over two weeks the results suggest that in the accelerated condition three to four days might have been sufficient to complete withdrawal.

In Italy naloxone and naltrexone have been used to accelerate lofexidine or clonidine detoxification on an outpatient basis. A full opiate-blocking dose of naltrexone was reached on day three when lofexidine and clonidine were discontinued and patients were invited to continue with naltrexone on a maintenance basis to prevent relapse.[119] Lofexidine seemed preferable to clonidine because it was associated with significantly less severe mood disturbance and withdrawal symptoms (which were minimal by day three), and did not lower blood pressure. Following detoxification there was no significant difference in withdrawal symptoms between the two groups and about the same proportion of patients completed detoxification (17 or 18 out of 20 in each group) and progressed to naltrexone maintenance (about three-quarters). All patients were men.

Benefits from any form of pharmacologically accelerated detoxification must be balanced against some limited evidence that even very brief non-accelerated inpatient withdrawal can have good completion rates and worthwhile short-term post-detoxification outcomes. In the USA 116 patients completed intake procedures and were followed up after a three-day inpatient detoxification.[120] The programme used clonidine to ameliorate withdrawal symptoms plus group therapy intended partly to enhance motivation, encourage longer term treatment, and prevent relapse. Many patients were excluded due to medical or psychiatric conditions which might interfere with follow up and 34 left before intake to both study and treatment could be completed. However, the follow-up rate for the remainder was over 90% and the subjects were typically unemployed, indigent heroin and cocaine users in poor medical health with a long history of addiction and of addiction treatment who spent large sums on illegal drugs and had committed crimes on most days in the past month. In the six months after treatment about a third returned to daily heroin use; the two-thirds who did not included a quarter who had remained abstinent. Despite nearly 80% trying heroin again after treatment, the average number of days on which the drug was used was more than halved and there were similar reductions in alcohol and cocaine use. Spending on drugs and illegal incomes fell to between a third and a fifth of pre-intake levels and there was a similar fall in the number of days on which crimes were committed. Improvements were partly accounted for by the follow-on treatment engaged in by about a quarter at one month and about 15% at later follow-up points. However, even those who did not later enter treatment improved to some degree following detoxification, and entry into such treatment was, after all, one of the objectives of the detoxification episode.

Across all relevant studies completion rates for unaccelerated detoxification using lofexidine or clonidine average about 60–70% and for short-term methadone (up to 21 days) just below 60%. In both cases inpatient treatment completion is about 70% while outpatient completion is just 35% (methadone) or 53% (lofexidine or clonidine).[121] Treatment completion rates for buprenorphine detoxification (in most studies inpatient) range from 65% to 100%.[122]

The lack of conventional detoxification facilities in some areas and waiting lists in others make a high throughput method such as rapid detoxification seem more attractive, especially if lighter sedation methods prove acceptable and effective.[123]

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1 Lawental E. "Ultra rapid opiate detoxification as compared to 30-day inpatient detoxification program – a retrospective follow-up study." *Journal of Substance Abuse*: 2000, 11(2), p. 173–181.

2 "Remained abstinent since detoxification" - table 1.

3 "Self reported current heroin use" – p. 176.

4 On page 177 "abstinence status" is defined as "abstinent from heroin vs. not abstinent."

5 "Abstinence status at follow up,

6 Defined as self reported current heroin use and/or other drugs use" – p. 176.

7 29% rapid and 46% conventional had been rejected for army service. Of the rest, 38% and 30% respectively had completed. Therefore of all patients, 0.38 x (100-29) and 0.3 x (100-46) had completed service.

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11 Gossop M., *et al.* "Treatment retention and 1 year outcomes for residential programmes in England." *Drug and Alcohol Dependence*: 1999, 57, p. 89–98. For inpatient units typically offering detoxification and relapse prevention services the median stay was 15 days while the intended length of stay ranged from two to five weeks. This implies that at least half the patients left before completing the regime. However, probably most will have completed the acute detoxification phase. In the same units the retention period associated with the greatest reduction in opiate use was 28 days; only 20% of patients stayed for at least this period.

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