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▶ A comparison of methadone, buprenorphine and alpha2 adrenergic agonists for opioid detoxification: a mixed treatment comparison meta-analysis.

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A new methodology to combine the results of relevant studies suggests buprenorphine has the edge over methadone among the main medications used to help dependent patients complete withdrawal from heroin and allied drugs.

Abstract For the first time this meta-analytic review applied a new methodology to combine results from comparisons of the main medications used to help dependent patients comfortably complete withdrawal ('detoxification') from opiate-type drugs like heroin. It enabled the analysis to include *indirect* comparisons between two medications which, even though they may not have not been compared head-to-head, have been compared to the same third medication. The principle is similar to the logic that if A is better than B, and B is better than C, then A must also be better than C. It means more trials can contribute data to the comparison, potentially giving a more secure indication of the preferable medication.

A search for English-language reports in (among other sources) major databases up to May 2006 yielded 23 trials which randomly allocated in all 2112 participants to at least two detoxification options based on tapering doses of the opiate-type drugs methadone or buprenorphine, or the non-opiate medications clonidine or lofexidine. The latter subdue some of the body's reactions to the sudden absence of opiates. The criterion of effectiveness was completing the detoxification programme. Completion data was available from 20 trials; four compared methadone and clonidine, two methadone and lofexidine, three methadone and buprenorphine, eight buprenorphine and clonidine, one buprenorphine and lofexidine, and two clonidine and lofexidine.

The main difference made by extending the analysis to indirect comparisons was to elevate the relative performance of buprenorphine. Taking all the data in to account, it

was estimated that for every 100 people who completed a methadone detoxification, 164 would complete if prescribed buprenorphine. In contrast, across the three head-to-head comparisons the medications seemed roughly equivalent, with a very slight difference in favour of methadone. Other than this, results confined to direct comparisons were in the same direction and of the same order of magnitude as results based on both direct and indirect comparisons. Across the fuller dataset, from 1.6 to nearly four times as many people completed procedures based on the two opiate-type medications (buprenorphine and methadone) than those based on either of the non-opiate medications (lofexidine and clonidine). Of the two non-opiate medications, lofexidine was preferable, 150 people completing for every 100 prescribed clonidine.

However, the range within which the true estimates might have lain was usually so wide that the reverse conclusion could not confidently be eliminated. Only the comparisons between buprenorphine (the most effective medication) and clonidine (least effective) met conventional criteria for statistical significance, indicating that these differences were highly unlikely to have occurred by chance. Despite this uncertainty, there was an 85% chance that buprenorphine really did lead to the highest completion rates of all the medications, a 12% chance for methadone, and near zero for lofexidine and clonidine.

The author concluded that the opiate-type medications were both probably more effective than clonidine and lofexidine and that (with a greater degree of uncertainty) buprenorphine seemed the most effective of all at promoting completion of a detoxification programme.

FINDINGS This summary is expanded on in the background notes.

Like the featured analysis, another major meta-analysis also found that buprenorphine probably has the edge over methadone in terms of completing withdrawal, and confirmed that it is considerably superior to non-opiate medications; details in background notes. Despite the uncertainties, possibly greater effectiveness allied with the fact that overdose deaths are less likely with buprenorphine than methadone seems sufficient to make it clinically preferable. What might tip the balance for a service is that buprenorphine costs more than methadone. Set against this, buprenorphine programmes can be completed in a shorter time and in some inpatient studies, after a single dose, saving costs (1 2 3 4; details in background notes).

Unless there are overriding contraindications, choice of medication in respect of an individual patient can largely be based on their informed preferences. British studies (1 2; details in background notes) have found that patients who choose what the featured analysis found to be one of the least effective medications (lofexidine) do as well as those who choose the most effective (methadone or buprenorphine), possibly because the least dependent and perhaps most motivated patients opt to do without opiate-type medications.

British guidance (1 2; details in background notes) adds that patients already being prescribed methadone or buprenorphine on a maintenance basis or to stabilise them prior to detoxification should normally continue with the same medication. In particular, the transfer from methadone to buprenorphine has to be carefully managed to avoid precipitating withdrawal symptoms, though it may offer a way to detoxify patients who find stopping methadone difficult. Though this should not override patient preference, the

guidance sees clonidine and lofexidine as most suitable for patients with low levels of dependence or who may not be dependent at all, advice which means these medication should have a bigger role in detoxifying young people.

Completion of detoxification was the criterion used by the featured review, and of course this is an appropriate aim for such a procedure. However, completion is a mixed blessing. The guidance cited above warns that the loss of tolerance (the ability to tolerate higher doses after becoming used to regularly taking a drug) following detoxification heightens the risk of overdose and death if patients return to opiate-type drugs, especially if at the same time they drink or take benzodiazepines. This risk is greatest among patients who complete the detoxification phase of the programme (1 2 3), highlighting the need to carefully select and prepare detoxification candidates and to invest in aftercare. Programmes which achieve high rates of completed withdrawal through isolation (such as inpatient programmes and those which precipitate withdrawal under sedation) seem particularly likely to lead patients who are not yet ready for an opiate-free life to lose their protective tolerance. Ironically, outpatient programmes which test the patient's resolve in real-world conditions may be safer because relapse is more likely to occur before tolerance is eliminated. See fuller discussion in background notes.

As the author acknowledged, the review was limited to the main medications used in conventional medicine. There is evidence that herbal remedies can ameliorate opiate withdrawal symptoms to roughly the same degree as the non-opiate drugs lofexidine and clonidine. Also, two types of detoxification programmes were not explicitly analysed by the review. First are the rapid procedures conducted normally in a single day under anaesthesia or sedation, during which withdrawal is precipitated by an opiate-blocking drug, typically naltrexone. These can ensure that a high proportion of patients complete detoxification and start treatment (usually itself based on naltrexone) to sustain abstinence, but many relapse meaning the longer term benefit relative to conventional methods remains unclear. Second are the regimens common in Britain which reduce doses of methadone over several months and not according to a pre-determined protocol. These are largely unresearched except for the NTORS study in England, which recruited patients in 1995. It found these often became maintenance regimens in all but name and (especially for more severely dependent patients) were less successful at curbing heroin use and improving health, other drug use, and crime.

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▶ Background notes

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