


# DRUG & ALCOHOL FINDINGS *Research analysis*

This entry is our analysis of a study considered particularly relevant to improving outcomes from drug or alcohol interventions in the UK. The original study was not published by Findings; click [Title](#) to order a copy. Free reprints may be available from the authors – click [prepared e-mail](#). [Links](#) to other documents. [Hover over](#) for notes. [Click to](#) highlight passage referred to. [Unfold extra text](#)  The Summary conveys the findings and views expressed in the study. Below is a commentary from Drug and Alcohol Findings.

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## ▶ [Methadone induction in primary care for opioid dependence: a pragmatic randomized trial \(ANRS Methaville\).](#)

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*From France the first study to randomly allocate patients to start methadone maintenance either in primary care or at a specialist centre found primary care more attractive to patients, and no less effective at reducing street-opioid use and promoting engagement and retention.*

**SUMMARY** Methadone is in the World Health Organization's list of essential medicines due to its effectiveness in treating **opioid** dependence, preventing the spread of HIV, and improving adherence to antiretroviral treatment for HIV infection. Nevertheless, access to methadone remains limited, partly because of the risk of overdose during the 'induction' period in the first weeks of treatment when doses are being adjusted. In France as in most countries, methadone induction is confined to specialised substance dependence treatment centres, which can refer patients to primary care for continued treatment only after the end of a minimum 14-day induction. This means that in areas underserved by specialised centres, methadone treatment can be unavailable.

In response, the hepatitis plan of French national public health authorities included a 'pragmatic' (relatively real-world) trial as a basis for reconsidering primary care as an entry point for methadone treatment. Titled 'Methaville', the trial was designed both to evaluate the feasibility of methadone induction in primary care and to compare outcomes for these patients versus those inducted at a specialised centre. To replicate normal practice in France, patients could choose to change from their assigned setting after the induction phase. This means the trial was one of the difference made by the induction setting, not the setting for continued treatment over the follow-up year.

The main patient outcome was abstinence from 'street' opioids after one year of treatment. The data was analysed to assess whether there was evidence that primary care induction was inferior to specialised induction, determined by whether this outcome was at least 15% worse, a margin chosen to reflect willingness to accept somewhat lesser effectiveness in return for what it was thought would be a more attractive and engaging setting. One year was chosen as the primary follow-up point because by this time any possible effects of the induction setting would be manifest.

At ten sites in four areas with different drug markets and drug user practices/needs, the researchers recruited a physician in a specialised centre matched with nearby primary care physicians experienced and/or trained in care for opioid dependence, and whose patients included some potentially eligible for the trial. These physicians enrolled into the trial patients seeking treatment for opioid dependence, who were allocated at random to start methadone treatment either with one of the site's primary care physicians or at the specialist centre. Unlike primary care settings, specialist centres offered a multi-disciplinary assessment of the patient and on-site counselling, but might delay the first dose of methadone for a few days. By design, twice as many



### Key points

From summary and commentary

Patients in France seeking treatment for **opioid** dependence were allocated at random to start methadone maintenance either in primary care or at a specialist centre, after which they could switch settings.

Starting methadone maintenance in primary care was feasible and acceptable for both physicians and patients, no less effective than induction in specialised care in reducing street-opioid use and promoting engagement and retention, and more attractive to patients.

The trial substantially adds to research which suggests that not just induction, but ongoing treatment in primary care is usually at least as effective as treatment in specialist centres.

However, outside the context of a trial which may select and train its prescribers, in normal practice in the UK there is some evidence that induction in primary care carries a higher risk of overdose death than induction at specialist clinics.

patients were allocated to primary care to more adequately assess risk of overdose. Patients had to be adults not prescribed methadone for at least a month, or receiving buprenorphine but needing to switch to methadone for medical reasons such as side-effects or misuse of the medication.

All the physicians underwent a one-day training course to standardise methadone induction practices. Trial guidelines stipulated that the starting dose should on average be 30 mg and not exceed 40 mg, and increase over at least 14 days by 10 mg every two to four days until the dose was stabilised. During this period consumption of the medication was supervised at the centre or at a pharmacy, and then continued only for patients thought at risk of overdose. Strategies to prevent overdose during induction included physician training, strict supervision of consumption, and fostering close collaboration between health professionals involved in the study, including pharmacists.

Among the 57 physicians who agreed to participate in the study, from January 2009 to December 2010, 32 enrolled at least one patient who could join the study. Of the 221 patients enrolled in the study and randomly allocated to the induction settings, 185 actually started treatment. Typically they were men in their early 30s and about half were switching from buprenorphine. About half were employed and half had injected drugs, but most not in the past four weeks. Snorting up the nose was the usual route of administration.

For the main analysis all the randomly allocated patients were included – a so-called ‘intent-to-treat’ analysis. The 26 who did not start treatment and any who dropped out of the study or did not provide the relevant data were considered to have returned to use of street opioids. Another analysis included only the 162 patients re-interviewed at month 12, a variety of ‘per protocol’ analysis. Because this was a pragmatic, real-world trial intended to test the acceptability and feasibility of the treatment as well its effectiveness, the intent-to-treat analysis was primary.

## Main findings

Among the 221 randomly allocated patients, 27% allocated to specialised induction refused it compared to 5% allocated to primary care, a statistically significant difference in the acceptability of the settings. During induction, at specialist clinics five patients dropped out of the study versus two in primary care. After induction 10 patients inducted at specialist clinics dropped out of the study versus 16 in primary care. Overall, 31% of patients inducted at specialist clinics left the study early compared to 12% inducted in primary care.

Engagement and retention in treatment was best when patients had been allocated to induction in primary care. At specialist centres 65% of randomly allocated patients completed induction versus 94% in primary care. Of those who at least started their induction, 69% at specialist centres were still being treated at the study’s centres at the 12-month follow-up compared to 88% inducted in primary care. Of the 43 patients who completed induction at specialist clinics, 18 later switched to primary care, but just one of the 145 inducted in primary care made the reverse transition.

Also superior was suppression of illicit or ‘street’ opioid use, identified when patients either admitted to recent use or were presumed to have returned to opioid use by virtue of having left the study or not supplied the relevant data. Among all the randomly allocated patients, 12 months later 33% allocated to specialist centres had not used street opioids during the previous month compared to 55% allocated to primary care. On this, the study’s main effectiveness indicator, induction in primary care was not only ‘not inferior’ to induction at specialist clinics, it was significantly superior.

When the analysis was confined to patients actually followed up at 12 months, after induction in both kinds of settings two-thirds of patients had not recently used street opioids, confirming that on this key measure induction in primary care was not inferior to induction at specialist clinics.

Patients had been followed up also three and six months after being allocated to the induction settings. Taking all these results into account, across the 12 months there was no significant difference in abstinence from street opioids, though the results favoured primary care.

No overdose was observed during the induction phase, and apart from one intentional overdose, no severe adverse events were reported throughout the trial.

Halfway through the 12-month follow-up patients were asked about their relationships with and satisfaction with their physicians. Patients inducted in primary care were significantly more satisfied with the explanations of their care provided by their physician.

[Another report](#) on the results of the same trial found that patients’ accounts of being imprisoned and of offences committed (in particular, buying or selling drugs – other offences were rare) fell substantially within the first six and three months of treatment respectively. These trends were seen among both patients transferring from buprenorphine and those initiating maintenance treatment after a break of at least a month.

## The authors’ conclusions

For both physicians and patient, methadone induction in primary care is feasible and acceptable. It is no less effective than induction in specialised care at reducing street-opioid use and promoting engagement and retention in treatment. On the contrary, it is more effective and more likely to attract and engage patients and be given high satisfaction ratings, though given the ability to switch settings, after completed induction retention is similar regardless of the induction setting.

The induction process used for primary care in this study may be of interest to other countries seeking to extend access to methadone treatment. Using primary care as an entry point has greatly contributed to the scaling-up of treatment for opioid dependence in countries such as the UK. It also helps 'normalise' care for drug users. However, in France at the time of the trial primary care already played an important role in treatment for opioid dependence. Where this is not the case, results may differ.

Though this was the first study to randomly allocate patients to specialist versus primary-care induction, its results are broadly consistent with other research indicating that patients receiving methadone in primary care have comparable treatment responses in terms of retention and opioid use to those treated at specialist clinics.

Given the safeguards incorporated in the trial, no fatal or non-fatal overdoses were known to have occurred during induction.

**FINDINGS COMMENTARY** Within the unique French context, which for opioid dependence relies mainly on widely available primary care treatment, the featured study offers the most rigorous demonstration yet that induction onto methadone need not be more risky in primary care than at specialist centres. It confirms that primary care can form the foundation for a more engaging and therefore more effective treatment system, and suggests that risks entailed in induction need not be a barrier to expanding access to methadone treatment via the primary care route. It substantially adds to a body of research (nearly devoid of randomised trials) which suggests that not just induction, but ongoing treatment by primary care doctors (especially those experienced and/or well trained and guided) is usually at least as effective as treatment in specialist centres.

However, trials or the usual practice documented in studies may by design or in practice exclude the most complex, challenging or risky cases from primary care, and sometimes too, primary care services have been supported by specialist services. Outside the context of a trial which may select and train its prescribers, in normal practice in the UK there is some evidence that induction in primary care carries a higher risk of overdose death than induction at specialist clinics.

These comments are expanded on below.

### About the study

Recruitment and retention [are essential](#) to the lifesaving impact of methadone maintenance, [which acts](#) more like an on/off switch than a permanently transforming cure. On this score, starting treatment in primary care seemed far superior in the featured study. Taking into account those who refused induction, 33 of the 66 patients allocated to specialist induction were not in the study's treatments a year later (and were assumed to have returned to use of street opioids) versus 26 of the 155 allocated to primary care, equating to a loss of 50% versus 17% of patients.

If all the patients who later switched between settings remained in the study, 77% allocated to specialist induction either switched to primary care or left the study compared to 17% allocated to primary care – an upper-bound indication of a large difference in the acceptability of the settings. The main uncertainty over the interpretation of these figures is how many patients presumed to have left treatment actually did stay in or return to treatment, but not with the study's physicians. In the French context, they might have moved to other GPs.

### Continued maintenance in primary care

While this study was about induction, continuing methadone treatment in primary care can also be as effective in reducing illegal drug use (and on other measures) as treatment in specialist clinics. Among the studies are some from the UK. Based on a national sample of 240 patients starting treatment in England in 1995, one [found](#) that two years later patients treated by GPs and those treated at specialist clinics had improved substantially and usually to roughly the same degree. What differences there were favoured the GPs, whose patients had made significantly greater reductions in use of stimulants and non-prescribed benzodiazepines and greater gains in psychological health, and tended to stay in treatment longer. The results do not

seem to have been due to differences between the types of patients treated at the two types of settings. However, patients who could not be followed up were also the heaviest users of heroin, potentially the patients who might have benefited most from treatment at a specialist centre.

Like this national study, local studies in Britain and studies elsewhere (1 2 3) have compared GP-based and clinic-based treatment of patients treated through normal channels rather than by random allocation, meaning differences or similarities in outcomes may be due to differences in the types of patients seen rather than the effectiveness of the treatments. Among these studies is [one from France](#), where about 70% of opiate-dependent patients receiving buprenorphine maintenance from GPs were retained for at least six months compared to about 60% at addiction centres. The difference was not statistically significant and neither were the differences in outcomes at the two settings, which included substantial improvements in drug and related problems and in quality of life. However, patients seen by GPs tended to be less entrenched in their habits. Nevertheless, whether the medication is methadone or buprenorphine, this study plus the featured study provide no evidence that in France maintenance at primary clinics is any less effective than at specialist clinics.

In addition, in 1999 a [small trial](#) in the USA recruited opioid-dependent patients who for at least the past year had been in methadone maintenance at a specialist centre without evidence of illicit drug use or significant untreated psychiatric comorbidity. For six months they were randomly allocated to continue in treatment at the centre or to transfer to specially trained primary care physicians. Perhaps partly due to the small sample, there were no significant differences in illicit drug use, physical and mental health and social functioning, or use of health, legal, or social services, though the important measure of drug tests indicative of illicit opiate use favoured the specialist centre (38% of patients versus 50%). There was, however, one statistically significant finding: 73% of primary care patients compared with 13% who stayed at the centre thought the quality of their care was excellent.

Supplemented by some solely of primary care treatment (1 2), these studies confirm that retention and outcomes (including crime, risking blood-borne disease, illegal drug use, health and mortality) are usually no worse – and sometimes better – than at specialist clinics.

### **In normal UK practice primary care may be less safe than specialist treatment**

Though the featured study rightly highlighted the UK as a country which permits methadone induction in primary care, in 2016/17 in England just 19% of opiate users in treatment were [recorded as having been treated](#) in primary care at some time during the year. [UK guidelines](#) on treatment of problem drug use make it clear that induction onto methadone is complex and risky, requiring multiple factors to be taken into account to avoid overdose due to cumulating blood levels of the drug. At the same time there is need to prescribe sufficient doses to retain the patient and to get as quickly as possible to a dose which eliminates use of illegally obtained opioids, [itself a risk factor](#) for overdose. Avoiding these risks during induction requires judgement perhaps best gained by experience and frequent and careful monitoring of patients – both most likely to be available or feasible at specialist clinics.

To the degree that these risks and demands deter GPs from involvement in the treatment of opiate addiction, this highly accessible and relatively attractive route into treatment will be barred, acting as a brake on the proportion of patients in treatment and therefore its ability to save and improve lives. Internationally the UK has a good record in engaging high-risk opioid users in treatment, but in Europe six countries [may be doing better](#). Topping the league is France due a huge expansion in buprenorphine-based treatment in primary care, suggesting that there is room for improvement in the UK via that route. A big difference is that methadone is the mainstay in the UK. However, the featured study shows that induction onto methadone in primary care need not be less safe or less effective than in specialist services, and therefore that the risks entailed in induction need not be a barrier to expanding methadone treatment access via primary care.

However, “need not be” is not the same as saying that the risks will always be equivalent. The featured study took place within the internationally unique French context, highly reliant on widely accessible and widely used primary care services and on buprenorphine, and it recruited experienced or specially trained practitioners who were

offered further training and standardised induction procedures incorporating safeguards against overdose. Comparing the findings of two studies – one primarily of [specialist services](#), the other of [primary care](#) treatment – it seems that in normal practice in the UK, primary care induction may not be as safe as induction in specialist clinics. Both studies evaluated routine practice outside the context of a trial. [Unfold !\[\]\(2e897e890e69d81eae4503a8342c36b0\_img.jpg\) the supplementary text](#) for more.

[Close supplementary text](#)

Between 2005 and 2009, in England the study which drew its sample mainly from [specialist addiction treatment](#) services matched identifiers in two sets of routinely collected records to establish whether people recorded as having received treatment for their dependence on opiate-type drugs had died from drug poisoning. A similar, but UK-wide study, sampled [general practices](#), analysing records of substance misuse patients who had been prescribed methadone or buprenorphine between 1990 and 2005.

Both studies found the death rate while out of treatment was over twice as high as while in treatment. But there was also a major difference. At the equivalent of 6.9 deaths per 1000 people over a year, the absolute rate of death while in primary care treatment was far greater than the 2.6 figure in specialist services. One reason would have been the inclusion of Scotland with its much greater rate of drug-related deaths per head of population. Others that the primary care study analysed all-cause mortality, not just overdose deaths, and spanned a time when supervised consumption had yet to become the norm and when injecting was more common.

More worrying was that the greater rate of deaths among primary care patients was partly due to an elevated death rate during the first four weeks of treatment – the induction period. At this time the patients were 2–3 times more likely to die over a given time period than later in treatment. At specialist services, the reverse was the case – the first four weeks were actually safer than subsequent treatment, possibly because specialist services were at these times more likely than GPs to enforce medically supervised consumption of medication during induction.

[Close supplementary text](#)

See these [Effectiveness Bank notes](#) for more on research on primary care opiate addiction treatment and its advantages and disadvantages. For more studies, run [this search](#) in the Effectiveness Bank.

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