


analysis

This entry is our analysis of a study added to the Effectiveness Bank. 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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► Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial.

Haight B.R., Learned S.M., Laffont C.M. et al.

Lancet: 2019, 393, p. 778–790.

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In the new form of extended-release injections with effects lasting a month, the opioid medication buprenorphine was found to suppress illegal opioid use more effectively than a placebo, reinforcing its promise as a possible “game-changer” in opiate addiction treatment.

SUMMARY Several drugs target the **opioid** receptors in the brain which lead to opiate-type effects. Some like methadone generate positive opiate effects (opioid ‘agonists’), others like naltrexone (opioid ‘antagonists’) occupy the receptors, preventing opiates having any effect while themselves not causing these effects. **In between** is buprenorphine, a ‘partial agonist’ which, like methadone, can alleviate opioid withdrawal, reduce craving, and attenuate the subjective effects of taking further opioids, but which also has antagonist properties. Methadone is likely to be abused, diverted to other people or to the illicit market, or misused, and often has to be taken under clinical supervision. To avoid precipitated withdrawal, naltrexone can be started only after the patient has completely withdrawn from opioids. In contrast, buprenorphine can be titrated to patients’ withdrawal symptoms, easing the transition into treatment.

Patients who take buprenorphine daily dissolved under the tongue (‘sublingual’) suffer from large fluctuations in blood levels and may not take the medication as prescribed. Having to take medication every day is also a constant reminder of their condition, and like methadone, it can be diverted, misused or abused, including being taken inadvertently by children, concerns which limit its use.

In theory the risks and limitations of daily buprenorphine are largely overcome by extended-release versions of the medication injected weekly or monthly under the skin (a subcutaneous ‘depot’ formulation). Approved by the US Food and Drug Administration, the product tested in the featured study was designed to sustain buprenorphine levels over an entire month sufficient to attenuate the subjective effects of taking further opioids like heroin, with little or no risk of diversion or skipping doses.

Key points

From summary and commentary

Like methadone, the **opioid** medication buprenorphine suppresses illegal opioid use and retains opioid-dependent patients in treatment.

However, buprenorphine regimens based on products dissolved under the tongue risk patients not taking the medication or it being passed on (‘diverted’) to other people or sold, and may require daily attendance at a clinic or pharmacy.

Injected every four weeks, extended-release buprenorphine can largely avoid these risks while being more convenient for patients. In this randomised trial, it was substantially more effective than a placebo at retaining patients and suppressing illegal opioid use.



To test whether the promise of depot buprenorphine was realised in practice, the manufacturer sponsored a study comparing two dose

regimens against placebo injections in the treatment of patients with (according to the latest US diagnostic system, the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*) an opioid use disorder, including those who might previously have been classified as dependent on heroin. Other important aims were to assess depot buprenorphine's safety and acceptability to patients, and whether blood levels of the medication were related to outcomes.

For the study, 36 US treatment centres recruited adults seeking treatment for moderate or severe opioid use disorder, who seemed to the researchers or doctors to be appropriate candidates for the buprenorphine treatment on offer. Other requirements were: not recently in treatment for opioid use; not also problem drinkers or problem cannabis or cocaine users whose drug tests revealed current use of these drugs; to test free of barbiturates, benzodiazepines, methadone, or buprenorphine; not suicidal or suffering medical or psychiatric illnesses which may threaten the participant or their ability to complete the study; not unable to comply fully with study requirements. The typical patient was a white, non-Hispanic man in their late 30s or early 40s who had been using opioids (41–51% by injecting) for on average 11 years; over 40% had also been using cocaine and around half cannabis.

In ratios which gave a them a greater chance of being administered active medication, over 24 weeks a resulting 489 patients included in the analyses had been randomly allocated to be injected every four weeks with either:

- six 300 mg doses of extended-release buprenorphine;
- two 300 mg doses of extended-release buprenorphine followed by four 100 mg doses;
- near identical placebo injections with no active medication.

Starting all the buprenorphine patients on a high dose was intended to quickly establish blood levels of the drug which would prevent opioids taken 'on top' having any effect, and then either to maintain these levels with 100 mg doses or build up to higher levels by continuing with 300 mg doses in case some patients needed these to control their opioid use. No top-up doses of sublingual buprenorphine were available; patients who seemed to need these had to leave the study. The four-weekly injections were started after a lead-in period of a week or two during which patients were stabilised on sublingual buprenorphine; only those who could tolerate buprenorphine and for whom it at least partially mitigated opioid withdrawal and craving progressed to the main phase of the trial. Throughout, all patients were offered weekly counselling, seemingly of the kind which might typically be provided by keyworkers in buprenorphine or methadone programmes.

To give patients time to stabilise and the treatments a chance to take effect, the measures on which they were assessed were those taken from the fifth week of the of the medication phase to the final 24th week. During this time weekly drug tests and patient interviews both had to signify opioid abstinence for this to be registered. It was assumed that missing records would have indicated opioid use. Primarily at issue was whether abstinence was more common among patients allocated to buprenorphine injections. Other measures such as craving and withdrawal severity were also assessed, and missing values estimated based on previous assessments.

Main findings

Nearly two-thirds of patients allocated to buprenorphine injections (64% on high doses; 62% lower doses) completed the study, almost twice the 34% allocated to placebos. The biggest gap in reasons for leaving was the treatment not working; this applied to 27% of leavers allocated to placebos but just 5% allocated to buprenorphine. Premature termination among placebo patients began to exceed those of patients injected with the active medication soon after the injections started. By the time of the second four-weekly injection the gap was already substantial and did not greatly increase thereafter. Associated with this (since missing tests or reports were considered opioid-positive), by four weeks into the randomised phase of the trial documented abstinence from opioids was also substantially less common among placebo patients and remained so.

The upshot was that on average, patients allocated to buprenorphine were known to be abstinent from non-prescribed opioids over 40% of the time (41% high dose; 43% low dose) compared to just 5% among placebo patients. Nearly 30% of buprenorphine patients (29% high dose; 28% low dose) registered abstinence in at least 80% of the weekly assessments, considered successful treatment. Both differences were highly



statistically significant and very unlikely to have been due to chance. Findings were similar for reports of craving for opioids and withdrawal symptoms, both by week two and thereafter consistently more severe among patients administered a placebo. There were no signs that relatively successful suppression of opioid use among buprenorphine patients had led them to escalate their use of other drugs.

In contrast to the buprenorphine–placebo differences, at no point were there anything other than minor differences between patients allocated to lower versus higher doses of the active medication, and among both 88% of those left at the end of the study were satisfied with their medication. This was despite the fact that (as expected) the average level of buprenorphine in the blood was about twice as high among patients administered 300 mg injections throughout versus those transferred to 100 mg from week nine of the 24 weeks. On both doses blood levels **attained or exceeded** those considered necessary on average to control both withdrawal and craving and attenuate the experienced rewards of taking illicit opioids, though some patients might require more.

In each of the three sets of patients, up to 5% experienced a serious adverse event and/or an event which led them to terminate treatment which emerged during treatment. There was one opioid overdose, a non-fatal incident among the placebo group. Injection site problems were more common among buprenorphine than placebo patients, but still affected only a small minority and were generally transient and non-serious, prompting just one of the buprenorphine patients to leave treatment. Body function test results revealed no unexpected safety issues, and at no time did patients initiate suicidal ideation or behaviour not already present.

An analysis which differentiated missing data from urine test and self-reports positively indicative of opioid use showed that missing data did not fully account for the findings, and clearly supported the superiority of extended-release buprenorphine over placebo. This analysis also showed that nearly all placebo participants who left treatment prematurely had been using opioids in the previous weeks, while buprenorphine patients who left had often been opioid-negative. Analyses excluding missing assessments due to drop-outs also showed the superiority of the active treatments versus a placebo.

The authors' conclusions

Extended-release buprenorphine offers a new treatment option for opioid-use disorder, especially when there are concerns about the patient's compliance with treatment, diversion, misuse of medication, or that the patient will skip doses or not take doses on time, opening up a window for illegal use. These formulations may also be particularly appropriate when there are children in the home who might take stored medication, when patients fear daily dosing might reveal they are in treatment or that their medication might be stolen, or for patients averse to taking medications every day. On extended-release buprenorphine, substantial proportions of such patients may benefit from abstinence from non-prescribed opioids, relief of withdrawal symptoms, and control of opioid craving, without needing medication daily or supplemental sublingual buprenorphine.

Unlike methadone and other buprenorphine products, extended-release buprenorphine offers the advantage of once-monthly subcutaneous administration, and unlike extended-release injectable naltrexone, buprenorphine is not contraindicated in individuals still physically dependent on opioids or who are in acute opioid withdrawal, and does not require an opioid-free period before initiating treatment. The featured study suggests that both the 300 mg and 100 mg doses have a safety profile similar to that of sublingual buprenorphine. As predicted from other studies, transferring to the 100 mg dose still maintained blood levels sufficient to control opioid use, though future research may show higher doses work better for some patients, particularly those injecting opioids.

These results were obtained from patients averaging over a decade using opioids, many with the multiple problems to be expected in routine practice. The requirement that they respond reasonably well first to sublingual buprenorphine is in line with best practice, though it meant that whether the 160 patients excluded on this basis would have benefited from the depot injections was not tested.



FINDINGS COMMENTARY Among the recruited US sample, this study conclusively demonstrated that monthly buprenorphine injections retain opioid-using patients and suppress their opioid use more effectively than a placebo when both were supplemented by keyworking-type counselling. It was the sole trial of clinical efficacy which in 2017 helped persuade the US Food and Drug Administration that the medication was safe and effective enough to [allow its marketing](#) in the USA under the trade name Sublocade, specifically for the treatment of “moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal [eg, sublingual] buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days”.

A [companion report](#) on the same sample of patients effectively showed that as well as helping reduce non-prescribed opioid use, compared to a placebo extended-release buprenorphine led to a healthier and more normalised life for the patients. The indicators included employment, mental and physical health, quality of life, and use of medical services other than the study's treatments.

Further information on the study emerged as part of the US Food and Drug Administration's [approval process](#). This suggested a 'ceiling' effect similar to that found for sublingual buprenorphine, such that suppression of opioid use reached its maximum at around the blood levels thought by the manufacturer to be needed for effective treatment (levels reliably achieved by the medication tested in the study) and no greater suppression resulted from higher levels. However, these results across the entire sample may not apply to patients who used opioids by injection. Among these patients, suppression of opioid use occurred at much higher doses than among non-injectors, suggesting (the difference was not statistically significant) that for effective treatment they need higher doses of the medication, such as those provided by sustaining the 300 mg dose.

Alternative long-acting products match efficacy of sublingual buprenorphine

Publication of this demonstration of the absolute (ie, relative to no active medication) efficacy of depot buprenorphine follows that of [another US study](#) which demonstrated the superiority of a depot buprenorphine product to daily sublingual buprenorphine. As would be expected, in this study the depot formulation's advantages were slight and much less apparent than in the featured study. Sponsored by a different pharmaceutical company, the extended-release formulation used in this trial differed from that used in the featured trial.

In both studies, patients [had been selected](#) to be appropriate for buprenorphine-based treatment and to be able to follow the intended treatment, which usually they did. Nevertheless, there was considerable room for improvement in outcomes. Assessments generally revealed illegal opioid use, and for most patients treatment did not succeed according to the studies' criteria. These results may seem modest, but the featured study showed that without the active medication, relapse to illegal opioid use (either established by interviews/tests or presumed due to these being missed) was near universal, despite weekly counselling.

As the researchers pointed out, instead of among the relatively compliant patients in the trials, extended-release injections would seem to have their greatest potential among less stable patients – those unlikely to take daily doses and perhaps even less likely to regularly attend a pharmacy or clinic for consumption to be supervised.

As well as injections, a long-acting delivery vehicle for buprenorphine has been developed in the form of small rods containing the drug which are inserted under the skin in a minor operation. Effects last up to six months. An [early trial](#) and [later similar trials](#) convincingly demonstrated that among opioid-dependent patients the implant is superior to a placebo implant at



suppressing unauthorised opioid use, craving and withdrawal symptoms, and at promoting general clinical improvement, though at the cost of a large proportion of patients experiencing adverse effects and discomfort at the implant insertion site.

This much is to be expected in the comparison of an active versus an inactive medication. As with buprenorphine injections, the more telling comparison is with conventional buprenorphine treatment using daily sublingual preparations. Among patients entering treatment the two [were found](#) virtually equivalent in the suppression of opioid use and in the risk of serious adverse events affecting the patients. Among patients already stabilised on a relatively modest dose of sublingual buprenorphine who were no longer using illicit opioids, switching to buprenorphine implants (plus placebo sublingual buprenorphine) [proved](#) only slightly but significantly more effective at maintaining abstinence from illicit opioids than continuing with sublingual buprenorphine (plus placebo implants). Serious adverse events were no more frequent among the active implant patients, though unwanted reactions at the implant site were common, affecting nearly a quarter of patients.

An “enriched” patient sample?

The featured study's encouraging finding that being partially prevented from experiencing an opioid ‘high’ did not lead to other forms of drug use has to be seen in the context of its exclusion of patients most likely to have taken this route. For similar reasons, the superiority of depot buprenorphine over placebo might not be as great among the general run of patients.

Of the 1187 applicants screened for suitability for the study, 522 were excluded at this stage, most commonly because they had recently used barbiturates, benzodiazepines, methadone, or buprenorphine. The US Food and Drug Administration's [review](#) highlighted the fact that “Only patients who could tolerate buprenorphine, reach a stable buprenorphine dose within about 2 weeks, and comply with returning to the study site through the run-in period could be enrolled. One-quarter of the patients who entered the run-in period were ultimately not randomized ... this enriched population may give a more optimistic picture of the product's efficacy than can be expected in a general population”. They went on to suggest that despite this, “superiority to placebo is not expected to be affected”. However, this seems over-optimistic. Among placebo patients, so infrequent was abstinence from illegal opioids that on this measure they could not get much worse, meaning the gap between them and patients allocated to buprenorphine could have been substantially narrowed had the study recruited a less “enriched” set of patients. How severe was the substance use of applicants who did join the trial seems in question. Though on joining all had been assessed by the study as exhibiting at least moderately severe opioid use disorder, according to their own accounts only 15–17% had a history of drug dependence, while over 80% registered the lesser classification of drug “abuse”.

Concerns over industry sponsorship

Without specifically casting doubts over the featured study, it does fall squarely within a class of trials over which concerns have been expressed – those sponsored by pharmaceutical companies with strong commercial interests in the results. In general it [has been found](#) that “Research sponsored by the drug industry was more likely to produce results favouring the product made by the company sponsoring the research than studies funded by other sources.” It [has been claimed](#) that various sources of bias in favour the pharmaceutical industry's products mean “research funded by industry undermines confidence in medical knowledge”.



Such concerns cannot be proven to be valid in the case of the featured study, but neither can they be dismissed. All but one of the authors were employees of, or consultants to, the pharmaceutical company which sponsored the study, and which under the trade name Sublocade [markets](#) the extended-release product it tested. The sponsor had much to gain from positive results, and much to lose from negative ones or other impediments to uptake of the medication (1 2). [According to](#) investment analysts, "Indivior wants Sublocade to offset the declining sales of Suboxone" as generic equivalents undermine the Suboxone market. This is part of the context for a study in which, as the featured report records, the same company [designed the study](#) and had a role in data collection, data analysis, data interpretation, and writing the report.

One way industry-sponsored research has resulted in a positive result for its products [is through](#) the choice of a weak comparator – for example, a placebo – rather than an alternative active medication or the standard treatment for the complaint in question. [According to](#) an analyst of pharmaceutical industry trials, industry-backed studies often compare a new drug to placebo or a second-line agent which makes it easier to get a positive result for a new drug. "My preference would be to compare with what's recommended as the current best therapy."

Among the widely implemented UK treatments for opioid addiction, "current best therapy" [would have to refer](#) to oral methadone, with sublingual buprenorphine second. [Already known](#) is that a comparison of a different depot buprenorphine product versus sublingual buprenorphine produces much less convincing support for the depot than the comparison with a placebo conducted by the featured study. Yet to be published is a comparison between extended-release buprenorphine and the usual pharmacotherapy for opiate addiction in both the USA and the UK – oral methadone maintenance. Such comparisons are of greater relevance to the practical issue of whether commissioners and services should consider rebalancing current daily-dose opioid maintenance regimens towards depot buprenorphine, but are also less likely than a placebo comparison to produce results in favour of the new formulations.

In the featured report the rationale for not comparing depot with sublingual buprenorphine referred to the artificiality of such trials, which would require all patients to take either daily buprenorphine or daily buprenorphine placebos and therefore to attend the clinics more frequently than required by monthly dosing. A sublingual buprenorphine placebo would indeed have distanced the trial further from intended usual practice, though in the US context it [has proved possible](#) to compare depot and sublingual buprenorphine without requiring attendance more often than required for the depot injections.

Extended-release buprenorphine could be "game-changer"

Regardless of any limitations of trials to date, there seems no doubt about the advantages for the patient of not having to attend daily or several times a week at pharmacies or clinics in countries where this is recommended or required for treatment with oral methadone or sublingual buprenorphine. Importantly also, it is likely that extended-release buprenorphine [will be associated](#) with fewer overdose deaths overall, including those due to its being diverted to people other than the intended recipient, and [probably too](#) fewer deaths among the patients themselves. The main doubts are over depot buprenorphine's



ability to attract and retain patients in treatment and satisfy the needs of high-dose opioid users. Though in theory the greatest benefit [should accrue](#) to the least stable patients and those least able to resist interrupting treatment in order to take illegal opioids, in practice these same patients may reject depot buprenorphine or rapidly drop out of treatment and seek an alternative, especially in areas where oral methadone is easily available.

Though not the product tested in the featured study, under the trade name Buvidal, on 20 November 2018 a different form of an extended-release buprenorphine injection [was authorised](#) to be marketed in the European Union for the treatment of opioid dependence. In turn, Buvidal [was licensed](#) to be marketed in the UK, and in February 2019 [NICE](#), the UK's health product assessor, issued [guidance](#). [NICE's](#) experts noted that the recommended maximum dose of Buvidal may not be enough for some patients, and that the cost of providing this medication greatly exceeded sublingual buprenorphine and oral methadone, though there would be savings due the reduced need for supervised consumption. Some of the experts considered the preparation most likely to be suitable for patients who might sell or pass on other opioid medications, where there were concerns about these being stored at home, difficulties adhering to daily supervised administration, or for patients who are stable on a therapeutic dose of sublingual buprenorphine or live in areas without easy access to a pharmacy.

Professor Sir John Strang of King's College, London – arguably the most influential clinician and researcher in the drug treatment sector in the UK – welcomed the advent of Buvidal [as a possible “game-changer”](#) in opiate addiction treatment: “Patients with opioid dependence in Europe are in great need of new and more effective medications that can improve treatment outcomes and quality of life. Buvidal weekly and monthly subcutaneous injection depots could become a game-changer in opioid dependence treatment by improving adherence and reducing the burden, stigma and risks of daily treatment.”

His research centre has explored how potential patients in London feel about the prospect of long-acting buprenorphine implants and injections ([1](#) [2](#) [3](#)). They felt they would appreciate having a steady level of opioids in their bodies and the stability, freedom and normalisation of not having to attend pharmacies and take medication daily, but were also concerned about loss of control over when to take their medication, change the dose, or stop. Some felt daily medication gave their lives structure, something to do and people to interact with, and would miss the highs of ingesting an opioid. With weekly, monthly and six-monthly products available, [one study](#) focused on duration. Not surprisingly, the six-month option aroused the strongest reactions for and against. Feelings were that longer duration formulations might be more suitable for patients who want to avoid thinking about drugs and drug use, were keen to evade the stigma of substance use, and seeking time and space to enjoy some ‘normality’ and establish non-drug focused routines and structure. In contrast, shorter duration formulations might be better for patients new to opioid maintenance,



concerned about the safety and reliability/effectiveness of the products, interested in having a 'break' from street opioids without necessarily stopping altogether, or who need contact with services to monitor and support them and provide structure. Usefully, some of the findings [were used](#) to construct a checklist of nine topics related to the patient's concerns and goals for treatment and how they feel about different delivery mechanisms for medications for treating opioid use problems, intended to help patient and clinician come to a joint decision on which is most suitable.

Dr Mark Greenwald, the corresponding author of the featured study, [has talked](#) about the study and the advent of what he considers a "transformational" treatment.

Thanks for their comments on this entry in draft to research author Professor Mark Greenwald of Wayne State University School of Medicine in the USA and Melinda Setanoians of Indivior UK Limited. Indivior sponsored the featured study and markets the medication it tested. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

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STUDY 2017 [Effectiveness of injectable extended-release naltrexone vs daily buprenorphine–naloxone for opioid dependence: A randomized clinical noninferiority trial](#)

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STUDY 2019 [Efficacy and cost-effectiveness of an adjunctive personalised psychosocial intervention in treatment-resistant maintenance opioid agonist therapy: a pragmatic, open-label, randomised controlled trial](#)

STUDY 2010 [The SUMMIT Trial: a field comparison of buprenorphine versus methadone maintenance treatment](#)

STUDY 2009 [Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial](#)

STUDY 2012 [After the randomised injectable opiate treatment trial: post-trial investigation of slow-release oral morphine as an alternative opiate maintenance medication](#)

STUDY 2014 [Treatment retention, drug use and social functioning outcomes in those receiving 3 months versus 1 month of supervised opioid maintenance treatment. Results from the Super C randomized controlled trial](#)

DOCUMENT 2017 [Drug misuse and dependence: UK guidelines on clinical management](#)

REVIEW 2014 [Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence](#)

STUDY 2014 [Methadone induction in primary care for opioid dependence: a pragmatic randomized trial \(ANRS Methaville\)](#)

