This clinical update focuses on Espranor® (bup-lyo), the lyophilized (rapid-disintegrating) buprenorphine tablet for opioid use disorder (OUD), produced by Ethypharm, which has been available since January 2017.

This update evaluates the evidence base for Espranor®, and compares it to the most commonly prescribed buprenorphine formulation for OUD, sublingual buprenorphine (bup-SL). Three papers reporting on different aspects of a single phase 2, open-label study are summarised, and then followed by commentary and a wider discussion about the clinical implications of this novel buprenorphine formulation.

This is a timely clinical update, given the recent 700% cost hikes of sublingual buprenorphine. Many services have already started prescribing Espranor®, largely driven by the need to offset the impact of the large price rises. It is therefore vital that the evidence base is scrutinised so that professionals and patients are able to make safe, informed decisions about care.

**Randomised comparison of a novel buprenorphine oral lyophilisate versus existing buprenorphine sublingual tablets in opioid-dependent patients: a first-in-patient phase ii randomised open label safety study.**

Strang J., Reed K., Bogdanowicz K., Bell J., van der Waal R., Keen J., Beavan P., Baillie S., & Knight A. (2017) European Addiction Research, 23(2): 61-70. doi: 10.1159/000456612. [Click here to read.](#)

This landmark phase 2, open-label randomised study tested the safety of bup-lyo vs bup-SL. Opioid dependent subjects (n=36) were randomised to commence buprenorphine maintenance with either bup-lyo (n=23) or bup-SL (n=13). Treatment comprised a dose titration period (days 1-7), a maintenance period (days 8-14), and an extension period (days 15-29) when bup-lyo subjects were switched to bup-SL. Measurements of safety included respiratory function, medication hold and dose adequacy, withdrawal symptoms, tablet disintegration times, and treatment retention. Pharmacokinetics for plasma buprenorphine and norbuprenorphine, an active metabolite of buprenorphine primarily responsible for the respiratory depressant effects, were also measured.

The median time for tablets to completely disintegrate was 2 minutes for bup-lyo and 10 minutes for bup-SL. Subjects in both groups were titrated to similar maintenance doses - 10.8mg for bup-lyo and 9.6mg for bup-SL - and no statistically significant between-group differences were observed in withdrawal symptoms, craving, adequacy of hold, or respiratory function. 81.8% of bup-lyo subjects (n=18) and 90.9% (n=10) of the bup-SL group reached their maintenance dose by day 3. No serious or severe adverse events (AEs) occurred though more treatment emergent AEs (TEAEs) were seen with bup-lyo (mostly mild). Retention across the study was 87% in bup-lyo and 77% in bup-SL, though this different was not statistically significant.

The authors concluded that bup-lyo disintegrated rapidly and that this may enable wider buprenorphine prescribing where supervision of dosing is required. No clinical difference between medications was observed and no increased respiratory depression occurred with bup-lyo. Pharmacokinetic studies found substantially increased bioavailability of buprenorphine (though not norbuprenorphine) with bup-lyo relative to bup-SL.
for a subset of participants (n=11) and are reported more fully in paper 2 below.

**Norbuprenorphine and respiratory depression: exploratory analyses with new lyophilized buprenorphine and sublingual buprenorphine.**


This paper reports on the pharmacokinetic data of subjects (n=11) from a randomised open-label study and compares plasma buprenorphine and norbuprenorphine levels in opioid-dependent subjects taking either bup-SL (n=3) or bup-lyo (n=8). Measurements of respiratory depression (defined as cumulative duration of pulse oximetry [SpO2] < 90% over 30-minute periods) were taken post-administration.

The authors found that respiratory depression increased with corresponding exposure levels of buprenorphine, and particularly norbuprenorphine, and that a lower buprenorphine/norbuprenorphine ratio was predictive of respiratory depression.

Investigators found that the mean (SD) observed buprenorphine / norbuprenorphine ratio was higher for bup-lyo than for bup-SL.

In conclusion, analyses suggest that although bup-lyo has a higher bioavailability than bup-SL, there was no greater risk of respiratory depression. In accordance with animal findings, the authors suggest this is because the more complete oral absorption of bup-lyo may lead to higher buprenorphine levels and therefore a higher buprenorphine / norbuprenorphine ratio, thereby limiting respiratory depression. Norbuprenorphine levels were similar for both formulations as the concentration of this metabolite is determined by the total amount of buprenorphine absorbed both orally and gastrointestinally.

**Switching between lyophilized and sublingual buprenorphine formulations in opioid dependent patients: Observations on medication transfer during a safety and pharmacokinetic study.**


This paper describes the process of switching from bup-lyo to bup-SL for 20 subjects with OUD. After 2 weeks of titration and maintenance on bup-lyo (dose = 10.8mg/day ± 4.85mg), subjects were switched to an equivalent dose of bup-SL.

Authors found that while it can be hypothesized that due to its comparative suprabioavailability of buprenorphine, dosing with bup-lyo should be lower than bup-SL, this study showed that no dose adjustment was required when switching from bup-lyo to bup-SL. Plasma buprenorphine concentrations were higher with bup-lyo than with bup-SL, though norbuprenorphine concentration differences were not statistically significant, and no additional respiratory depression was noted upon switching. The authors note large inter-individual variability of buprenorphine pharmacokinetics. There was also an absence of clinical differences in vital signs and other adverse events when switching formulations.

**Commentary:**
Although the overall sample size is relatively small, one major advantage of this study is the inclusion of patients with co-existing physical and mental health disorders. Patients with mild to moderate depression, anxiety, hepatitis C, concurrent benzodiazepine use, and a history of alcohol use disorder were all included, provided severity was not likely to compromise the subject's ability to participate in the trial. It is a common limitation of clinical studies that the relative health of the participants is not representative of real-world patients, and so any results lack applicability to clinical practice. The investigators here have admirably included representative patients so that generalizability to clinical populations is improved.

The primary limitation of this study is its small and relatively homogenous sample. Although representative of the typical OUD treatment-seeking population in the UK (mostly white, male, and slightly older), the applicability of findings to females, non-white patients, and patients outside of the included age range (23-58 years) must be considered. Additionally the open-label, between-subject design represents further limitations and results in differences between groups and the potential risk of bias. Future non-industry sponsored, randomised controlled trials with adequately powered sample sizes and heterogeneous populations are required to replicate findings. Currently long-term efficacy and safety data are also lacking, and future research should aim to address these gaps in the literature.

Importantly, non-inferiority to bup-SL was demonstrated across a range of outcomes – treatment retention, withdrawal symptoms, cravings, subjective medication “hold”, and respiratory function. One could argue that when making decisions about the choice of medication based solely on cost, non-inferiority of the new product is key. However, Espranor® may also be superior to sublingual buprenorphine in a number of ways. Firstly, the speed at which Espranor® disintegrates reduces the amount of time required to supervise administration, thereby reducing the resources required and the associated cost. Secondly, the rapid disintegration may mean that Espranor® can be prescribed and administered in settings where supervised administration of bup-SL is difficult, e.g. custodial settings and busy community pharmacies. Thirdly, diversion and subsequent misuse of Espranor® is more difficult than with bup-SL. Patients often fail to fully benefit from opioid substitution therapy (OST) in clinical practice, with the authors noting approximately 50% of patients drop out of both buprenorphine and methadone treatment. This failure partly derives from non-adherence and diversion of supplies. Espranor® cannot generally be removed intact within 15 seconds of administration. Whilst this does not eradicate the risk of diversion completely it does vastly reduce it, and may even help to improve adherence to buprenorphine, allowing more patients to benefit in the long-term.

One could argue that Espranor® may be less likely than bup-SL to cause respiratory depression, due to its higher buprenorphine/norbuprenorphine ratio. The authors suggest that buprenorphine may only minimally depress respiration and may indirectly be protective against respiratory depression as it competes for receptor occupancy with norbuprenorphine, which is up to ten times more potent in inducing respiratory depression in animals. Therefore, potentially the suprabioavailability of buprenorphine seen with Espranor® did not cause respiratory depression because the buprenorphine competed with the active metabolite norbuprenorphine for receptor occupancy, resulting in a higher buprenorphine/norbuprenorphine ratio. As these observations are based on animal studies, and the limited human data from this study, more pharmacokinetic studies are required to explore and confirm these hypotheses.

With any novel formulation of an existing drug, there is the risk of formulation-specific side effects emerging, and pharmacovigilance is required. More AEs were reported for bup-lyo compared to bup-SL. The authors suggest that the open-label randomisation utilised in this study may have contributed to AE reports. Additionally the higher buprenorphine plasma levels with bup-lyo may have contributed to the higher reporting rate. The most commonly reported mild TEAEs for the bup-lyo group were headache (4 subjects, 17.4%) and oral hypoaesthesia (reduced sensitivity to sensory stimuli), which was experienced by 2 subjects on a total of 3 occasions at 5- and 10-minutes post-administration. These resolved within 20-60 minutes. Other moderate TEAEs included vomiting, arthralgia, hyperhidrosis, and nausea; all of which are synonymous with opioid
withdrawal, so potentially precipitated withdrawal was experienced by some subjects. Importantly no AEs were reported as severe and none resulted in withdrawal from the study. We must be vigilant for side effects of new medication so we can give information to patients and ensure they have realistic expectations of treatment, which may subsequently improve adherence.

Although the study allowed up to 7 days for titration and stabilisation on a maintenance dose of buprenorphine, the majority of bup-lyo and bup-SL subjects were successfully titrated to their maintenance dose by day 3. The same dose schedule was used for both formulations – 8mg maximum on day 1, in divided doses of 2-4mg, with increases on subsequent days up to a maximum dose of 24mg per day for bup-lyo or 32mg per day for bup-SL. Treatment was individualised with doses being administered according to subjects’ withdrawal symptoms and vital signs.

Of note is that 1 subject was stabilized on 20mg of bup-lyo. Espranor® is only licensed to a maximum daily dosage of 18mg, so any prescribing above this dose in clinical practice would be off-label. The typical treatment dose range of sublingual buprenorphine is 12-24mg per day, up to a maximum of 32mg. Assuming a 25-30% increase in bioavailability of Espranor®, when cautiously switching a patient from a dose of 32mg sublingual buprenorphine, one might use an equivalent Espranor® dose of 24mg (25% reduction). This of course is above the licensed maximum daily dose. Although this scenario is unlikely to occur frequently in practice, it is one that clinicians should be prepared for. And we must consider the possibility that Espranor® might not be a suitable alternative for patients requiring larger doses of buprenorphine.

Conversely, patients requiring doses lower than 2mg would not be suitable for Espranor® as it is only available in 2mg and 8mg tablets. This may be particularly relevant for patients who are detoxing from buprenorphine, and require doses lower than 2mg at the tail end of a detox. This phase of a detox can be psychologically challenging for patients, and many benefit from having very small incremental reductions in the last few days. This would have to be done with sublingual formulations, which may be disruptive for the patient, particularly if there are perceivable differences in bioavailability between formulations.

Future qualitative research should aim to explore patient perception of Espranor® and the perceived risks and benefits of this new formulation. The authors speculate that with more rapid absorption of Espranor® patients may experience an earlier perceived drug effect, which may improve treatment retention. This hypothesis warrants further investigation but first it must be determined whether or not the perceived drug effect of bup-SL influences patients’ adherence to treatment in current clinical practice. I would suggest that the slow disintegration of buprenorphine and the need to be supervised by a member of staff, which can be stigmatising for patients, is as important in influencing adherence to treatment. Another question posed by the authors is whether the use of Espranor® will lead to prescribing of lower doses or alternatively higher effective dosing. Nationally, on average, patients are not prescribed adequate doses of OST, so perhaps a new formulation with higher bioavailability will effectively optimise treatment and see increased retention and a better subjective experience of buprenorphine for patients. This is all speculative at this point, and only time will tell.

Finally it is important to emphasise that, although this study found that Espranor® is comparable to bup-SL on a range of measures, and it appears safe and efficacious, the two products are not bioequivalent and are therefore not interchangeable. Caution must be exercised when prescribing for patients with comorbidity and polysubstance use, particularly if using (prescribed or illicit) respiratory depressant drugs. Individualised treatment must continue to be the mainstay of treatment, and service providers will need to consider implementing local policies for switching between formulations. Although this study demonstrated a dose for dose switch could be made from Espranor® to bup-SL with no adverse effects, when converting from bup-SL to Espranor® prescribers may want to consider a dose reduction of 25-30% due to the greater bioavailability of Espranor®.

**Take-Home Messages:**
• Espranor® has a higher bioavailability of buprenorphine compared to sublingual formulations. This results in a higher buprenorphine/norbuprenorphine ratio, which may be protective against respiratory depression.

• Espranor® tablets disintegrate within approximately 2 minutes, in comparison to 5-10 minutes for sublingual formulations, and can generally not be removed intact within 15 seconds of administration.

• Espranor® and sublingual buprenorphine formulations are not interchangeable and prescribers may wish to consider reducing the dose when switching from bup- SL to Espranor®.

• Faster tablet disintegration has several potential benefits for patients and professionals – shorter post-administration supervision times resulting in reduced burden on resources and less stigma for patients, faster perceived drug effects, and improved adherence to treatment.

• Further research with larger heterogeneous samples is required to replicate findings. Long-term outcomes also require investigation, and qualitative research is needed to elicit patient perceptions of Espranor®.

Further Reading:

Summary of product characteristics
MHRA Public Assessment Report

Conflict of interest Disclosures:

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