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Hello colleagues,

"I want the shot so I can get off of it": Does injectable buprenorphine discourage treatment engagement compared to sublingual?

Injectable, extended release buprenorphine (XRB) has provided a much needed treatment option for OUD. It can help stabilize individuals unable to stabilize with sublingual buprenorphine (SL bup); it has transformed MOUD care in some carceral settings, seems more effective in stabilizing OUD in pregnancy, may avert possible dental impact of SL formulations, and provides freedom from daily medication that often comes with emotional layover related to having an SUD. And, anecdotally at least, it is increasingly viewed by patients as a way to come off of MOUD. This is a concern, as we don't have data to support this as a safe choice. In fact, we have experience, some data, and an OUD disease model which suggests that even a physiologically gentle taper is high risk.

This study assessed OUD treatment retention among patients in a multi-location outpatient clinic in Maryland. It compared drop out among those who got at least one dose of XRB with matched controls who received only SL bup. ***It showed a median time to dropout of 269 days for XRB patients compared with 389 days for SL bup- a four month difference*** *- which is both statistically ($p<0.001$) and clinically significant. In a subgroup analysis (not prespecified), the authors found this difference was driven by those who transitioned to XRB in the first five months of treatment.*

This was an observational cohort study which means there could be unmeasured confounders, though the authors did use detailed clinical information to capture these (including a urine drug test derived risk score). This doesn't eliminate the chance of confounding but the importance of the effect warrants attention. And while we need more information about why people discontinued and what happened to them, this real-world study may be telling us that the immediate potential for withdrawal that comes with SL bup keeps people engaged, and so injectable, while helpful in many ways, may come with this potential down side. It may be worth having these discussions with patients as they start XRB, and including the concepts that cravings can be unmasked without physical withdrawal, that medications can provide impact months to a year after last injection and that the lower tolerance months out from an injectable dose means higher risk of overdose should there be a return to use.

More detail below. Thank you for reading,

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Title:

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Link: https://pubmed.ncbi.nlm.nih.gov/40468797/

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METHODS

This was a retrospective matched cohort study that looked at differences in time-to-dropout between extended-release buprenorphine (XRB) and sublingual buprenorphine (SL bup) in patients at a multi-location ambulatory SUD practice in Maryland from June 2019 to Feb 2024.

Inclusion criteria were age >18 living in Maryland with OUD. The only exclusions were methadone therapy or need for opioids for pain. Analyses were not preplanned.

At the first appointment patients completed a comprehensive behavioral health evaluation and started on SL bup. They were given a choice to transition to XRB at any follow up appointment. If patients went from XRB back to SL bup they were still evaluated in the XRB group.

Patients were seen weekly to monthly, in person, though its stated that telemedicine was used "when clinically appropriate". Urine samples were collected at each visit and analyzed with confirmatory testing (liquid chromatography- mass spectrometry). A single 7-day prescription was allowed for missed visits.

Treatment dropout was defined as >=90 days between the last appointment and the study's final observation date. It's unclear what happened to patients who returned after 90days as the study counted unique patients, but also stated that in Maryland a lapse in care of >90 days is a new treatment episode.

Patients were matched on demographics, medical and addiction history, time in treatment, and urine drug test derived risk scores which aim to capture the trajectory of medication adherence and substance use.

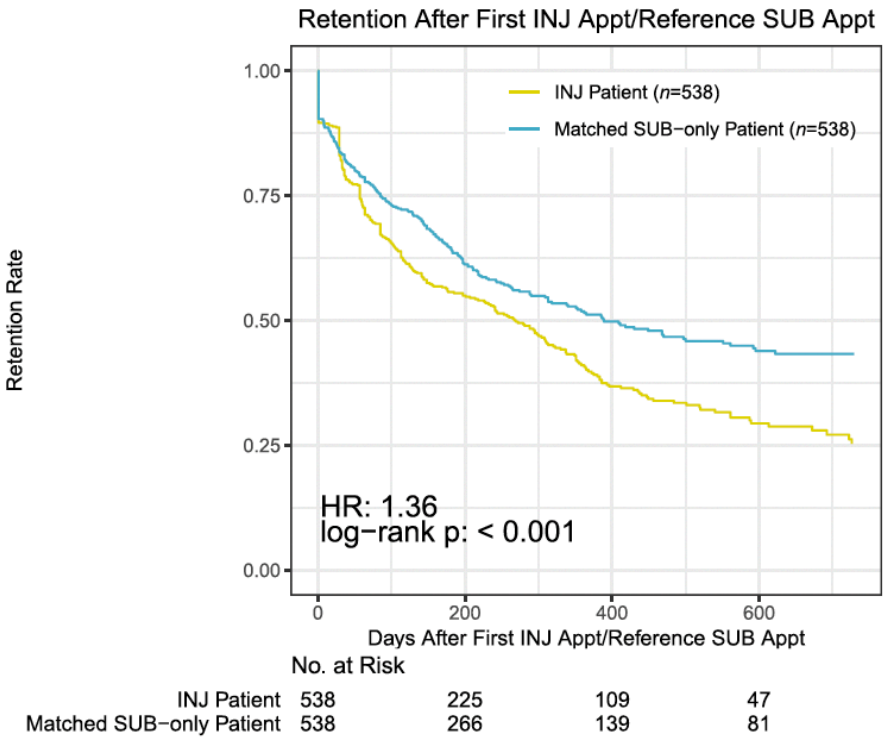
MAIN RESULTS

3609 unique patients were included. 538 (14.9%) had at least one XRB appt while 3071 (85.1%) remained on SL bup.

Average age was 35. ~1/3 were married. ~1/3 had more than a high school education. 3/4 had used nonprescription opioids and 10-13% used primarily by injection. Compared to SL bup patients, XRB patients were more likely to be female (47.2% vs. 38.7%; $P < 0.001$), less likely to be black (13.2% vs. 18.8%, $P = 0.002$), more likely to have education beyond high school (41.4% vs. 33.9%, $P < 0.001$), and slightly more insured though insurance rates were overall high (96-98%).

In the unmatched sample, the 538 XRB patients received their first injection at their sixth appointment (median) and stayed in treatment for a median of 15 appointments, compared to a median of 10 appointments for SL bup patients.

In the matched sample, the median time retained in treatment was shorter for XRB patients compared with SL bup (269 vs 389 days, or 8.9 months vs 13.0 months). This is represented over time, here:



In subgroup analyses, patients who started XRB earlier in treatment (<5 appointments) had a shorter time in treatment than for SL bup (177 vs 309 days, HR 1.52 p<0.001), but those who transitioned later did not (HR 1.16, p=0.22).

CONCLUSION

Among insured patients in Maryland, transition from SL bup to XRB was associated with significantly earlier drop out than among people who remained on SL bup.

COMMENTARY

This real-world finding merits attention as it may shift the balance of risk and benefit for XRB, especially among those who can get stable on SL bup. To better understand this signal, it would be helpful to know why people discontinue XRB and what happens to them when they do.

Why might it be that XRB patients disengage more readily? Possibilities include that:

- they have more severe disease and that could not be fully accounted for (in spite of a hearty propensity score matching), and/or
- XRB maintenance dosing was inadequate to suppress craving and people had a return to use (especially possible with early experiences in prescribing XRB), and/or
- due to the long acting nature of XRB, patients do not feel marked withdrawal, making taper easier, something patients often desire. [1]

A few additional things to note:

Overall, XRB patients in this cohort had longer retention than did patients on SL bup, but when comparing patients with similar risk profiles, the opposite was true. This is interesting in terms of informing how we process our clinical experience… **we may feel that our XRB patients do better, but it may be that we are not comparing them to patients with equal disease severity/risk**.

In a non-pre-planned subgroup analysis it seemed the difference between groups was driven by patients who started XRB in the first five months of care rather than among those who started it later.

What could explain this different between early XRB initiation and later?

- Perhaps it indicates a patient who did poorly with SL bup previously and either patient or provider made the XRB choice early on, selecting for a higher risk group
- Could it have to do with the ability to tolerate a transition early in treatment? The first few months of XRB are not always representative of how it will feel after achieving a steady maintenance dose (~4months). Before we had a lot of experience with XRB, that was not as commonly recognized and that may have impacted patients earlier in care more than those with longer stability.
- Or, is it an artifact in this study? Was there an XRB option that was cheaper or more convenient that patients left this practice for? Does insurance play in? ie, if a person loses insurance on XRB might they just stop coming because the cost is so high and the withdrawal is slower /more manageable while those on SL bup will stay in and make some sacrifices to pay for a lower cost treatment?
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Internal validity *(how likely are the study results what they appear to be for the study group)*

Unlike many of the insurance claims database studies that provide observational data, this data set came from a treatment program with a good deal of clinical information (demographics, urine drug test results, visit frequency, and medical history, time in treatment). They used this data to match patients, which seems like a fairly robust adjustment, but as with any observational study, is uncertain. **Was there something about the people who got XRB that made them higher risk for drop out that wasn't captured in the adjustment? Maybe.**

In support of that is the higher drop out among those who transitioned early. Perhaps they were less stable on SL bup, making transition a marker of instability that was not accounted for.

Still, the difference of four months between groups is significant and given the nature of XRB, there is biologic plausibility such that it could be due to the nature of the XRB.

Finally, we don't know if dropout means they left treatment. Its possible they went to an outside program.

External validity *(can these results be applied beyond the study)*

This may be a slightly lower risk MOUD group. In the limitations section, the authors share that most patients had initiated XRB after evidence of reduced use and consistent adherence. The descriptive statistics of this insured population suggest higher education and less IV use than among people with MOU as a whole. As such **these findings may not apply to highest risk populations, especially those who do not improve with the initial use of SL bup**.

We don't know about the doses or types of XRB used. Would the results be different if patients with cravings were maintained on a higher dose (ie, Sublocade 300mg monthly) or was that done? Was supplemental buprenorphine provided for the transition phase? If not, it might underestimate the benefit of XRB as it is evolving.

REFERENCES

1. Weinstein, Z. M., Gryczynski, G., Cheng, D. M., Quinn, E., Hui, D., Kim, H. W., Labelle, C., & Samet, J. H. (2018). Tapering off and returning to buprenorphine maintenance in a primary care Office Based Addiction Treatment (OBAT) program. *Drug and alcohol dependence*, *189*, 166–171. https://doi.org/10.1016/j.drugalcdep.2018.05.010