Andrea Truncali, MD, MPH **February 2026**

Hello colleagues,

The search for initiation strategies from fentanyl to buprenorphine continues. So far, there is one prospective trial (Donofrio, et al. 2024) and a few case series suggesting that the slower onset of injectable medications can help with this challenge. These findings have shaped the practice where I see patients such that those who have a COWs of at least 4 and no use for 12+ hours may choose to initiate treatment with 24mg of weekly injectable buprenorphine (XR bup). The risk of precipitated withdrawal with this approach is approximately 5% among those using fentanyl, and for those without buprenorphine on UDS, likely higher. However, the requirement to start treatment with only minimal withdrawal is often attractive to patients and may prevent missed opportunities to engage them in care.

Today's report describes a strategy to initiate injectable buprenorphine ***without requiring any withdrawal.*** *Patients received three injections in three days: 8mg XR bup weekly on Day 1, 16mg XR bup weekly on Day 2 and a choice of monthly injectable (128mg Brixadi or 300mg Sublocade) on Day 3.* ***With that strategy, 64% of the initial group received a second monthly injection; 83% of those who got a Day 1 injection went on to receive the monthly one.*** *There is no detail about those who didn't follow through with planned injection. In particular, there is* ***no quantification about the occurrence of precipitated withdrawal****, or any other adverse event except for the statement that severe withdrawal occurred "for some, particularly after the first monthly dose."*

So, more study is needed before we can inform patients about the risk vs benefit of this approach. In addition, the implementation of this strategy is complicated in that it requires:

- *Readily available XRB at multiple doses (as with buy and bill clinic stock, or where a pharmacy can reliably deliver medication within one day)*
- *Absence of administrative barriers (i.e., PAs, lack of insurance)*
- *Patient willingness to physically attend appointments for three days in a row (or have access to community-based provider visits as in this study)*

Because of these requirements, it is hard to imagine implementing this approach in a non-specialty environment, at least in the near future, but it is a promising step towards achieving buprenorphine initiation in the absence of withdrawal.

Read on for a more detailed look!

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Title: Injectable buprenorphine used to initiate treatment without prior withdrawal led to significant treatment retention but unclear incidence of severe withdrawal

Citation: Waters RC, Hoog J, Bell C, et al. Injectable-Only Overlapping Buprenorphine Starting Protocol in a Low-Threshold Setting. *JAMA Netw Open*. 2025;8(8):e2527016. Published 2025 Aug 1. doi:10.1001/jamanetworkopen.2025.27016

Link: https://pmc.ncbi.nlm.nih.gov/articles/PMC12357186/

Funding/Conflicts: No conflict. Data used was collected as a part of public health activities in Washington State.

METHODS

This is a retrospective cohort study that included individuals who chose an injectable-only initiation strategy from September 1 to November 30, 2024 at a low threshold OUD treatment program in Seattle. The program primarily serves patients experiencing homelessness or in supportive housing. Individuals included had been provided with initiation strategy options, chose this one, and had a weekly 8mg XR bup ordered and covered by insurance. (Almost all patients had Medicaid, or Medicaid/Medicare, and all injectable buprenorphine was provided without prior authorization by Washington State Medicaid.) Patients were excluded if they had consumed SL bup in the week prior to the first injection, were using methadone or were not actively using fentanyl.

Evaluation took place through the second MONTHLY injection which could occur as late as 45days from the first monthly injection.

Treatment was as follows:

Table 1. Summary of the Injectable-Only Overlapping Buprenorphine Starting Protocol[a]

Day	Long-acting injectable buprenorphine administered	Guidance for delayed buprenorphine injections[b]
1	Weekly 8-mg injection	NA
2	Weekly 16-mg injection	Offer the weekly 16-mg injection up to 2 d after the initial 8-mg injection before restarting.
3	Monthly 128-mg or 300-mg injection	Offer the monthly injection up to 3 d after the 16-mg injection before repeating a 16-mg injection. Consider restarting the full protocol if 7 d have passed since the 16-mg injection.

Patients were advised to continue using fentanyl “as safely as possible and carry naloxone” on Days 1 and 2. Clonidine, hydroxyzine, and ondansetron were offered for withdrawal symptoms. Supplemental sublingual buprenorphine was provided for withdrawal symptoms occurring 24hrs after the monthly (third) injection.

All medications were obtained from a local pharmacy where they could be ordered and delivered within one business day. Providers were able to administer medication to patients off-site in the community if needed.

Results:

Figure 1 shows outcomes.

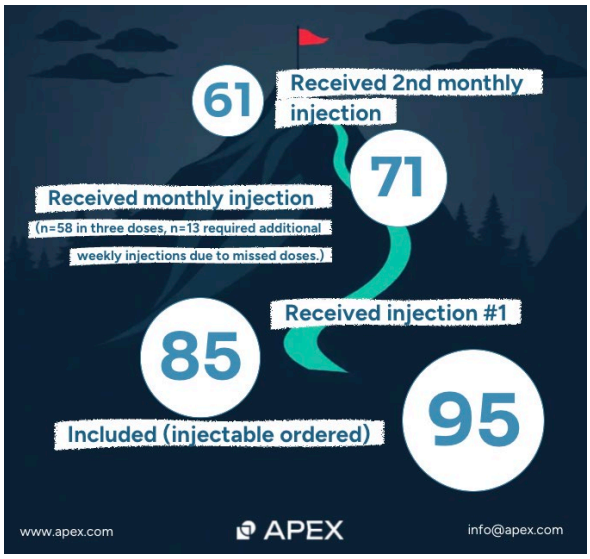

Figure 1: Number of patients at each time point.

64.2% (61/95) of those for whom XRB was ordered received a second monthly injection. 83.5% (71/85) of those who got the first injection went on to receive the monthly injection.

CONCLUSION

This three-dose protocol provides a promising strategy for XRB initiation without prior withdrawal in a system where XRB doses are readily obtained within one to two days of ordering. More data are need to understand the risks of precipitated withdrawal and other adverse events, and to directly compare with other low dose initiation strategies.

COMMENTARY

Internal validity *(how likely are the study results what they appear to be for the study group)*

This was a descriptive study of a new intervention, **without a comparison group**. Though it seems that 64% retention to medical treatment is a very good outcome in the population described, we don't know what would have happened with a similar investment and setting using an alternate strategy. The only indirect comparison is a report on sublingual low dose induction from SUD clinics in San Francisco which demonstrated 22% retention at 28 days (Suen et al, 2025).

Perhaps more challenging is the limited information about adverse events (i.e., overdose and precipitated withdrawal). Outcomes were not quantified but the authors did report that "many patients experienced mild withdrawal symptoms even after the initial 8-mg weekly injection, with patient-reported severe withdrawal occurring for some, particularly after the first monthly dose."

And though patients reported no buprenorphine in the week prior to injection, that was not verified by UDS. If recent buprenorphine exposure was underreported, that would overestimate the success of this strategy.

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

It is refreshing to have a study that applies to a vulnerable population such as this one. Still, this protocol can only be used in very limited circumstances, that is, in situations where:

- there is readily available XRB at multiple doses (as with buy and bill clinic stock or where a pharmacy can reliably deliver medication within one day)
- there are no administrative barriers (i.e., PAs, lack of insurance)
- patients can be seen for a clinical visit three days in a row

It is difficult to imagine this coming together in all but a specialty setting at the present time. In addition, the cost of this strategy is substantial due to the high costs of injectables and the need for multiple visits. This said, it is not beyond the cost of outpatient care for other serious medical conditions (i.e. chemotherapy infusion), and it is a strategy that allowed for successful initiation in 63% of a generally hard to treat population.

References

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