EVMS EM JC CRITICAL REVIEW FORM: THERAPY ARTICLES

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Citation:

Herring, A. et al., High-dose buprenorphine induction in the Emergency Department for treatment of opioid use disorder. *JAMA Network Open*, *4*(7). https://doi.org/10.1001/jamanetworkopen.2021.17128

Study Objective:
To examine the safety and tolerability of high dose (>12mg) buprenorphine induction for patients with OUD presenting to an ED. Primary outcomes were (1) the occurrence of precipitated withdrawal and (2) any other serious adverse event attributable to buprenorphine administration, including sedation, decreased respiratory rate, hypoxia, and/or naloxone rescue administration in ED or in the 24 hours after discharge.

Study Methodology:
Retrospective EHR review of patients aged 18 years or older treated with high dose (up to 32 mg) SL-buprenorphine at a large, urban, safety net ED between January 1, 2018, and December 31, 2018

GUIDE	COMMENTS
I. Are the results valid? Yes, researchers found that	
A. Did experimental and control groups begin the study with a similar prognosis?	N/A- no experimental versus control
1. Were patients randomized?	No- patients were placed in standard or high dosing pathways based on history, vital signs, physical exam, clinical judgement including withdrawal scoring system (COWS), evaluation of complicating factors (65 or older, AMS, pregnancy, methadone use, intoxication, post overdose reversal with naloxone, anticipated surgery, long term opioid therapy for pain, serious acute medical illness such as heart failure, liver failure, kidney failure, respiratory distress)
2. Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	N/A Retrospective study. Clinicians may have been biased in selecting who in their "clinical judgement" would be best suited for high dose treatment.
3. Were patients analyzed in the groups to which they were randomized?	N/A: However, patient data was compared in ranges of total buprenorphine dosing they were given.

4. Were patients in the treatment and control groups similar with respect to known prognostic factors?	The authors did not report on demographics, health history, severity of addiction between those who received standard vs. high dose Bup.
5. Were patients aware of group allocation?	N/A: patients were given increasing doses of buprenorphine based on providers' clinical judgement after initial standard dosing of 4mg-8mg and period of 30-60 minutes of observation for symptoms Also notable that the IRB granted a waiver of informed consent since data were deidentified and the study posted minimal risk to participants
6. Were clinicians aware of group allocation?	Clinicians would be aware of group, since they were escalating dosing of SL buprenorphine
7. Were outcome assessors aware of group allocation?	Yes. Two reviewers were involved in data abstraction; primary reviewer was blinded to the study aims and the secondary reviewer was blinded to abstraction of the primary reviewer. Assessors were given a standardized data collection form to minimize bias.
8. Was follow-up complete?	No follow up was conducted on individuals since this was a retrospective EHR case review, they did look for return visits in 24 hours to assess adverse outcomes but patients were not followed further than administration in the ED. One of their theories was that patients who get higher doses were more likely to follow up at outpatient settings however this was not tracked because of "Covid pandemic"
What are the results ?	• 391 unique patients representing 579 encounters High dose (>12mg) buprenorphine administered during 366 encounters (63.2%), 138 of which were greater than or equal to 28mg • No cases of respiratory depression, sedation or adverse effects reported • Median age 36 y/o 22.5% homeless • 5 cases of precipitated withdrawal (0.8%): 4 occurred after doses of 8mg buprenorphine (thus unrelated to high dosing pathway) and were treated with additional buprenorphine. The fifth case occurred after tolerating the initial dose of 8mg and had precipitated withdrawal after additional 24mg of buprenorphine, patient also had concurrent stimulant use • 3 life threatening adverse events: all unrelated to buprenorphine induction) • 53.5% not previously treated with BUP **Side effects were rare** • Supplemental O2 was required in those who received lower doses of BUP (p=.01)

	• Documented incidence of nausea or vomiting after buprenorphine was low (2 to 6% of cases) • LOS was also shorter in the higher dose group 3.5 vs. 2.3 hrs. (p=.002) • Advanced care providers were more likely to use high dose BUP (71% vs 28% p=<.001)
1. How large was the treatment effect?	Unsure: the type of study was limited on follow up since we are unable to know what exactly happened after patients left the ED and if they found outpatient treatment/adherence to prescription given for 16mg daily for maintenance treatment 10-18% of the patients treated were unsuccessful accessing follow up treatment after discharge and returned for repeat dosing in the ED
2. How precise was the estimate of the treatment effect? (CI's?)	N/A. No CI's given for statistics that were reported.
III **How can I apply the results to patient care?**	
1. Were the study patients similar to my patient?	Yes, study was conducted at a large urban ED with applicable patient population characteristics to NGH Achieving induction in a shorter amount of time plus a prescription for starting maintenance dosing through follow up would benefit patients by observing them in the ED through the higher risk portion of induction and giving patients
2. Were all clinically important outcomes considered?	Mostly. All patients were discharged in stable or improved condition after treatment No patients in the study had reported life threatening adverse events related specifically to high dose buprenorphine induction Mean ED stay of 2 hours, many encounters were in the low acuity side of ED No cost analysis provided
3. Are the likely treatment benefits worth the potential harm and costs?	Yes, they demonstrated low potential harm Cost accrued by the ED for higher amounts of buprenorphine given for high dose induction would possibly be a limiting factor

Limitations:

- Retrospective chart review Reliance on clinical documentation which is not standardized across providers and may not have included all the relevant data per encounter
- No prospective comparison of the high dose induction pathway versus traditional

- Unclear what the level of training was and what would be needed to provide a level of comfort in a broad range of clinicians
- No description of characteristics of group treated with high vs. standard dosing.
- The paper does not discuss this community's resources available for follow up or if they were given follow up appointments or were provided additional days of BUP because of homelessness or other socioeconomic difficulties.
- Study used monoproduct buprenorphine, some institutions may use buprenorphine-naloxone, which the larger amounts of naloxone could alter the clinical course

Clinical Bottom Line:
In theory, high dose induction appears to be safe and has low risks of adverse effects when applying this data, however significant outpatient barriers still exist including having X waiver physicians prescribing daily maintenance therapies, and community resources that patients can get to in a timely fashion