16 vs 24 mg: Beyond the Headlines

Greetings, colleagues!

In the era of fentanyl, we wonder, is more buprenorphine better? Or does having more medication on-hand feed other use disorders, the purchase of more fentanyl, and/or promote diversion? This retrospective study from the Rhode Island PDMP suggests that a 24mg dose and/or the treatment approach that travels with it, captures slightly more people than a 16mg dose and/or its associated approach. (ie, 59% discontinuation at 6 months compared with 53% for 24mg, or HR 1.2). It does not tell us what is the driving force behind the outcome – the dose or a key unmeasured confounder such as the prescriber's approach. Further it doesn't evaluate whether starting at a lower dose, like 12 -16mg, and moving to 24mg if needed, would produce a similar result, with less risk for overprescribing. Meanwhile, the overall retention rates (41-47%%) indicate that struggles at 16 or 24mg signal that it's time to start offering alternative solutions, like injectable medication or methadone.

Feel free to read on for the nitty gritty along with a little bit of background on the dose debates,

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Title: Prescribed buprenorphine doses of 24mg daily are associated with slightly higher treatment retention at 6months compared with 16mg daily.

Citation: Chambers LC, Hallowell BD, Zullo AR, et al. Buprenorphine Dose and Time to Discontinuation Among Patients With Opioid Use Disorder in the Era of Fentanyl. *JAMA Netw Open.* 2023;6(9):e2334540. doi:10.1001/jamanetworkopen.2023.34540

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METHODS

This was a retrospective cohort study using PDMP data of people in Rhode Island starting sublingual buprenorphine (bup) or bup/naloxone for OUD for the first time between Oct 1, 2016 and Sept 30, 2020. Anyone prescribed the included medications in the six months prior to Oct 2016 was excluded. For the primary analysis, only those initiated on doses of 16 and 24 mg were included (defined as: 16 mg (14 to <18 mg) and 24 mg (22 to <26 mg)) and anyone with a dosage change was "censored", meaning removed from the dataset after the change.

Each patient's follow up time was time to treatment discontinuation or 180 days, whichever came first. Treatment discontinuation was considered a gap in treatment of 27 days or more from the end of the last prescription. Analyses using Kaplan Meier and Cox Proportional Hazard were conducted, adjusting for informative censoring and some differences in patient characteristics.

MAIN RESULTS

Patient characteristics

57% of patients were age 25-44 and 61% were male. 47% had private insurance, and 33% Medicaid. Initial buprenorphine dose was 16mg in 50% of patients. Only 10% were initially prescribed 24mg. (21% were initially prescribed 8mg).

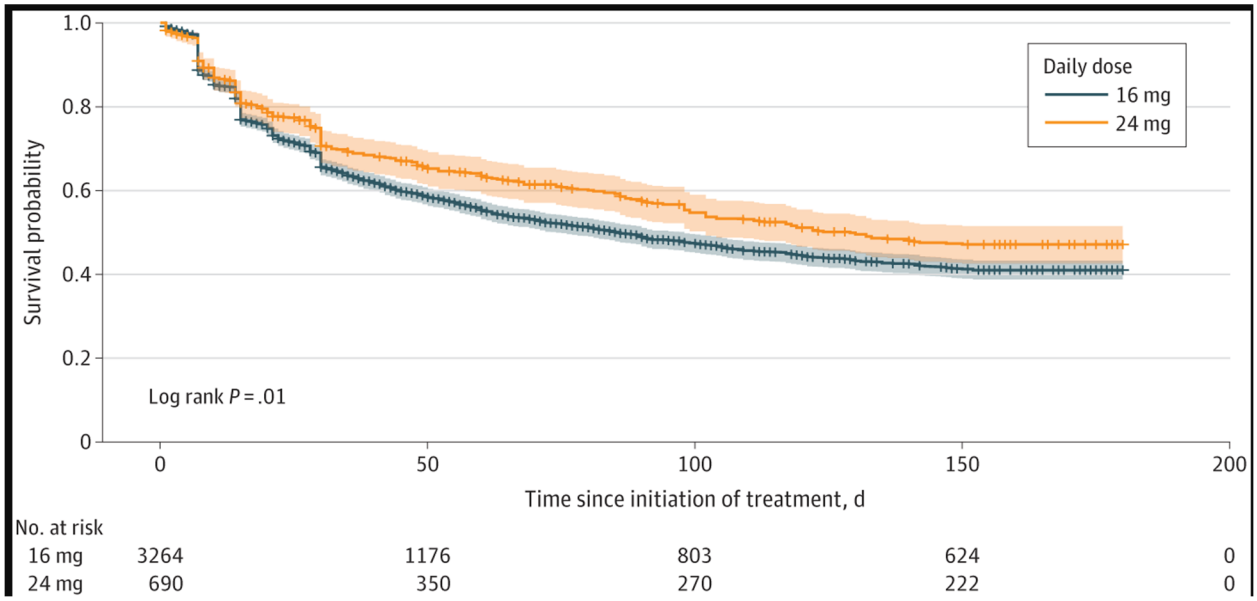
Those initially prescribed 16mg versus 24mg proved to have different characteristics. The 16mg group was younger and more likely to have initiated treatment in 2016-2018 than during the C19 pandemic/2019-2020 (70 vs 64%). Those prescribed 16mg were also slightly more likely to have Medicaid (36 vs 32%) and be female (49 vs 47%) but less likely to have a recent rx for benzodiazepines (14 vs 18%) or opioid (15 vs 19%).

Treatment Discontinuation

46% of patients were 'censored' during the 180 days of follow up because of a dose change at a median of 15days. Dose change was more likely to occur in the 16mg group (39 vs 26%), and the type of adjustment also differed between

groups (71% of the 16mg dose adjustments were increases, vs 90% of the 24mg group).

The investigators employed statistical techniques to attempt to account for the "informative censoring" (ie, censoring that introduces bias it relates to the likelihood of the outcome), ultimately finding that **treatment discontinuation occurred in 59% of the 16mg group vs 53% of the 24mg group.** Cox Proportional Hazard generated a disadvantage of 16mg with a Hazard Ratio of 1.2. (CI 1.06-1.37). Confidence intervals overlapped at approximately 120 days, suggesting either loss of power to detect a difference versus loss of effect of the dose differential.



The authors conducted other analyses, including one that evaluated only patients who were still engaged in treatment at day 30, and based inclusion on the dose prescribed on day 30 rather than day one. They report finding similar results to the primary outcome but note that the p missed statistical significance in this comparison (=0.0526).

Internal Validity Questions – What are limitations to bear in mind?

The analysis used here (survival, or time to event analysis), assumes that censoring (here, due to dose change) is not related to the likelihood of outcome (treatment dropout). Because that assumption is not met, the

authors tried to mathematically adjust (reweighting) to account for the potential bias -- but we can't know how effective that was.

In addition, the analysis tried to remove the effect of baseline differences between the 16 and 24mg groups but they can only adjust for available measures – ie patient characteristics (like age, insurance type, etc) and year of treatment initiation (such that pandemic effect was to some extent adjusted for). However, it did not account for provider characteristics including the fuzzy factor of practice style, such as threshold to stop prescribing or to impose additional requirements to continue treatment.

The authors tried to assess the impact of maintenance rather than starting dose with a 'stability analysis' that excluded the initial 30days, where most dose changes occurred. The survival curve looked similar to the primary analysis, but note that the difference just missed statistical significance.

Also, it's worth noting the overlapping confidence intervals later in the observation period (i.e. days 120+). This means that the two conditions look more alike over time and either suggests small numbers or that folks stable on 16mg have a similar prognosis to those stable on 24mg.

CONCLUSION

This retrospective study suggests that patients with OUD in the era of fentanyl, who are started and kept on 16mg of bup have slightly higher treatment discontinuation than those started and kept on 24mg. (absolute difference 6%, HR 1.2). The reason for this may be the dose but may also have to do with an unmeasured confounder, ie, lower barrier provider practice style. In addition, overall discontinuation at six months was 53-59%, suggesting that dose adjustment alone will be insufficient for most patients.

COMMENTARY

Some have previously made the argument that 24mg is superior to 16mg. This is largely based on Hser et al, 2014, which compared retention across doses up to 32mg, but **where medication administration was observed daily**. In that study there was a significant inflection point at 16mg such that every increase in mg beyond 16 was met with a less profound impact compared to the changes occurring from lower doses – that is, the effect of a

dose increase up to 16mg had a bigger effect than that same increase beyond 16mg. This matches with what I observe clinically, and also with opioid receptor saturation studies. In addition, the fact that medication taking was witnessed impacts the applicability to usual practice, as those who are actively using opioids are often not consistently adherent to buprenorphine. In another trial attempting to look at dose impact, Fareed et al, 2012 compared ''high dose" to "low dose" studies and concluded that "high doses" were better (at treatment retention) than lower doses. However, they defined high dose as 16-24mg, with the vast majority of studies at 16mg, and low doses were in the range of 4- 8mg.

Now however, we are in the era of fentanyl where it's biologically plausible that the potency of synthetic fentanyls may require more substantial blockade of opioid receptors. Can higher doses of buprenorphine achieve that in a clinically meaningful way? This study suggests that when providers initiate care at 24 vs 16mg, there is a slightly higher retention in treatment (47 vs 41%). **Was this because the providers who prescribed 24mg were also more likely to provide low barrier access, or was it the dose itself?** We don't know, but there are suggestions it might be the former. The comparison was between people prescribed 24 vs 16mg "at the get go". The practice of starting a patient out with 24mg of buprenorphine is probably more linked to the provider than the patient. This practice may indicate a provider who has a more harm reduction and generally lower barrier care approach to care than one who starts with the more typical dose of 16mg. And, the people started on 24mg were more likely to have their dose change be an increase than with the 16mg group.

Even so, let's say for a moment that the higher dose was the reason for the difference in retention. The study did not evaluate the usual approach of starting at 12 or 16mg/day and titrating up if needed. That approach may be just as good – as the sensitivity analysis looking at 24 vs 16mg at day 30 suggests. So, even if we believe it's the dose that made the difference, it does not necessarily follow that aiming for 24mg in all individuals will be beneficial. And while this data does provide some reassurance that we're not losing people from treatment with the higher dose, it doesn't look at all effects of overprescribing.

We want to help patients with OUD to initiate and maintain opioid abstinence, and we want to do it quickly. **This data suggests that a 24mg dose and/or the treatment approach that travels with it, captures slightly**

more people than a 16mg dose and/or its associated approach. It does not however evaluate whether the more typical practice of starting at a dose like 12-16mg, and moving to 24mg if needed, would produce a similar result, with less risk for overprescribing. Further, if patients are not stabilized by 16mg, it's warranted to begin discussions with them about injectable medication or methadone, as a focus on dose alone is unlikely to achieve the results we are hoping for.

References

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