HHS Public Access

Author manuscript

Drug Alcohol Depend. Author manuscript; available in PMC 2023 October 01.

Published in final edited form as:

Drug Alcohol Depend. 2022 October 01; 239: 109609. doi:10.1016/j.drugalcdep.2022.109609.

Buprenorphine & methadone dosing strategies to reduce risk of relapse in the treatment of opioid use disorder

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Abstract

Background: Although there is consensus that having a "high-enough" dose of buprenorphine (BUP-NX) or methadone is important for reducing relapse to opioid use, there is debate about what this dose is and how it should be attained. We estimated the extent to which different dosing strategies would affect risk of relapse over 12 weeks of treatment, separately for BUP-NX and methadone.

Methods: This was a secondary analysis of three comparative effectiveness trials. We examined four dosing strategies: 1) increasing dose in response to participant-specific opioid use, 2) increasing dose weekly until some minimum dose (16mg BUP, 100mg methadone) was reached, 3) increasing dose weekly until some minimum and increasing dose in response to opioid use thereafter (referred to as the hybrid strategy), and 4) keeping dose constant after the first 3 weeks of treatment. We used a longitudinal sequentially doubly robust estimator to estimate contrasts between dosing strategies on risk of relapse.

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Contributors: KER designed the study, supervised the analysis, drafted the paper, and revised the paper. NW and ATSG conducted the analyses and contributed to drafting the paper and revising the paper. ID contributed to the study design, analytic supervision, and revising the paper. MS, MF, SXL, JR, and EVN contributed to the data and to revising the paper.

Clinical trial registration details: This is a secondary analysis of three harmonized clinical trials.

Results: For BUP-NX, increasing dose following the hybrid strategy both resulted in the lowest risk of relapse. For methadone, holding dose constant resulted in greatest risk of relapse; the other three strategies performed similarly. For example, the hybrid strategy reduced week 12 relapse risk by 13% (RR: 0.87, 95%CI: 0.83–0.95) and by 20% (RR: 0.80, 95%CI: 0.71–0.90) for BUP-NX and methadone respectively, as compared to holding dose constant.

Conclusions: Doses should be targeted toward minimum thresholds and, in the case of BUP-NX, raised when patients continue to use opioids.

Keywords

opioid use disorder; buprenorphine; methadone; dynamic dosing; dynamic treatment; adaptive treatment; personalized medicine

Introduction

Opioid use disorder (OUD) continues to be a leading cause of morbidity and mortality in the United States (US),[1–4] and estimates suggest that its prevalence has increased during recent years of the Covid-19 pandemic.[5,6] The most effective treatments for OUD are long-term treatment with buprenorphine-naloxone (BUP-NX), methadone, or extended-release injection naltrexone (XR-NTX).[7] While on long-term medication for OUD, risk of death is estimated to decline by 50%, but remains unacceptably high given the approximately 20-fold increased risk of early death faced by those with OUD.[8] For methadone and BUP-NX, dose and dose adjustment are likely important factors in treatment effectiveness (dose is fixed for XR-NTX), but clinicians are tasked with making these decisions with little or no quantitative, evidence-based guidance.

Evidence suggests that dose is important for reducing risk of relapse and dropping out of treatment. Higher BUP-NX dosages more fully occupy opioid receptors[9,10] thereby blocking positive reinforcement of opioid use.[11,12] Higher BUP-NX dosages may reduce risk of drug use while on treatment[13] and may reduce risk of overdose.[12] Current guidance recommends BUP-NX dose of at least 16mg,[14] and trials have found that such a threshold is important for suppressing illicit opioid use during treatment.[15] However, treatment guidance currently discourages doses >24mg.[14]

Higher methadone doses (i.e., above 100mg daily) have been shown to provide better control of withdrawal symptoms between doses, likely through inducing tolerance. Better control of withdrawal symptoms reduces the reinforcing effects of illicit opioids, which may ultimately reduce opioid use.[16–19] Current guidance recommends methadone dosage of at least 60mg, and more typically, 80–120mg.[14] However, the effectiveness of dose increases beyond 100mg have not been well-studied.

Despite evidence of the importance of a “high enough” dose, underdosing for both BUP-NX and methadone treatment is common in practice[20] and implicated as contributing to suboptimal OUD treatment outcomes.[21] For methadone, although average dose has increased over time, in 2017, more than 40% of patients were still receiving methadone doses <80 mg.[21] Clinicians and patients may be reluctant to increase doses due to concern

about side effects (which can lead to medication discontinuation), or stigma attached to buprenorphine or methadone treatment (e.g., some providers equating MOUD with illicit substance use),[22] resulting in a treatment philosophy that the smallest possible dose should be used. Further, some patients can be successfully treated on doses that are far lower than the maximum,[14] and patients can often do well being maintained on a lower dose after the initial treatment period.[23,24]

Although there is some consensus on minimum dosage for methadone and BUP-NX, there is less consensus on how these minimum dosages should be reached (e.g., a dose increase schedule) and if/how dose should be tailored after the minimum is reached.[14] One recommended dosing strategy is to increase dose in response to individual-level opioid use until some maximum is reached, the rationale being that illicit use of opioids while in treatment, especially early in treatment,[25] is associated with risk of relapse.[26,27] Rudolph et al., 2021[28] recently demonstrated evidence in favor of such a dosing strategy, finding that increasing BUP-NX dose in response to an individual's opioid use reduced risk of relapse to OUD by 13% relative to a treatment strategy where BUP-NX dose remained constant.

Another recommended strategy is to increase dose early in treatment until some minimum threshold dose is reached, to more fully occupy opioid receptors (in the case of buprenorphine) and suppress withdrawal symptoms (in the case of methadone), and prevent opioid use early in treatment. Studies suggest that high buprenorhpine doses (e.g., 32 mg) may be necessary for full or near-full receptor occupancy and, consequently, clinical effect.[9] However, this upper range has not been tested; typical clinical doses are 10–18 mg.[20] Studies also suggest that higher methadone doses (e.g., >100 mg[17,29] or even 120–700 mg[30]) provide better agonist effects and lowers risk of relapse.

In summary, although there is consensus that having a "high-enough dose" is important for reducing relapse to opioid use, there is limited consensus on what this dose is or how it should be attained. While dose comparison questions can be addressed by randomized trials, such trials are di cult and expensive to conduct, and as a consequence, are rare. A recommended alternative strategy is to harness the naturalistic variation in dose and dose adjustments in relation to outcomes (in this case, abstinence from versus use of illicit opioids), in existing data to predict outcomes under different hypothetical dosing strategies.[31,32] We do so here, using existing data across three clinical trials with natural variability in methadone and BUP-NX dose/dose adjustments. We use a sequentially doubly robust and efficient estimator of longitudinal, time-varying treatments[33] to estimate the difference in risk of relapse under four dosing strategies, separately for BUP-NX and methadone: 1) where dose is increased in response to participant-specific opioid use, 2) where dose is increased weekly until some minimum threshold dose is reached, 3) where dose is increased until some minimum threshold dose is reached and then increased in response to opioid use thereafter, and 4) where dose is held constant after week 3 of treatment. Thus, we provide empirical evidence for the extent to which different dosing strategies for the treatment of OUD could reduce risk of treatment drop out and relapse.

Methods

Data and Sample.

We use data harmonized across three large randomized trials for OUD treatment that were part of the NIDA Clinical Trials Network (CTN): CTN0027,[23,34] Phase 2 of CTN0030,[35] and CTN0051[36] (we exclude the extended release naltrexone arm of this trial). Data was discretized into weekly increments for this analysis. All trials included patient treatment and monitoring over 12 weeks. Further details of the trials and their exclusion/inclusion criteria are in the Appendix.

We used data from N=1,863 participants who initiated treatment (by receiving at least one dose) with either BUP-NX or methadone. The Institutional Review Boards at the New York State Psychiatric Institute and Columbia University determined this secondary analysis of de-identified data to be non-human subject research.

Measures.

BUP-NX dose.—BUP-NX was used in all three trials, dispensed for participants to self-administer sublingually daily. Over the first 12 weeks of treatment, it was dispensed at weeks 0, 1, 2, 3, 4, 6, 8, 10, and 12 in CTN0051, dispensed weekly in CTN0030, and dispensed either daily or 3 times weekly in CTN0027. Dose and dose adjustment were based on clinical judgement in all three trials. In all trials, dose ranged from 2–32mg and could be increased in 2mg increments. In CTN0027 and CTN0051, clinicians were encouraged to increase dose in response to opioid use or symptoms of craving or withdrawal,[23,36] but this guidance was not always followed. In CTN0030, clinicians were encouraged to achieve rapid dose stabilization following induction.[35] Maximum daily dose for an individual during the outcome time-frame and prior to outcome occurrence was as follows by trial. For CTN0027: range=2–32mg, median=24mg, interquartile range (IQR)=16–32mg. For CTN0030: range=4–32mg, median=16mg, IQR=14–24mg. For CTN0051: range=4–32mg, median=16mg, IQR=12–20mg. We used the maximum dose reported for the week.

Methadone dose.—Methadone treatment occurred in CTN0027 and was dispensed daily with dose and dose adjustment based on clinical judgement. Study clinicians were instructed to have a maximum dose on the first day of treatment of no more than 40mg, to increase in 10mg increments, and to increase dosage in response to opioid use or symptoms of craving or withdrawal.[23] However, as was the case with buprenorphine, there was variability in the extent to which this guidance was followed. Maximum daily dose for an individual was: range = 10–270mg, median=75mg, IQR 60–100mg. As with BUP-NX, we used the maximum dose reported for the week.

Outcome.—The outcome was time to opioid relapse, occurring between 20 days post-randomization and prior to the end of 12 weeks of follow-up (the initial 20 days were excluded to preclude a relapse determination on the basis of opioids used for medically managed withdrawal (methadone, buprenorphine)). Relapse was operationalized as occurring on the last day of 7 days of daily use of non-study opioids, or on the first day of the fourth consecutive week of at-least-once-weekly use, where use is defined based on

1) urine drug screens, 2) Timeline Followback interviews,[37] 3) missed visits, and 4) refused urine screens, with additional details below.

As in the primary outcome papers for these trials, missed visits or refused urine samples were considered as positive for opioid use.[24,34,36] Although this likely introduces some measurement error, research suggests is a reasonable assumption.[24,38–40] For example, Hser et al., 2017[39] showed that individuals' long-term treatment participation trends are inversely related to their long-term opioid use trends. Weiss et al., 2011[24] and Weiss et al., 2015[40] showed that even long after the conclusion of the clinical trials, the majority of those not in treatment regularly use opioids. In Phase 1 of CTN0027, among those who were briefly treated (for 4 weeks) for prescription opioid use disorder, only 6.6% were not regular using opioids at 12 weeks of follow-up. The CTN0027 population had good prognostic characteristics,[24] so we would expect that percentage to be even lower for the general population of those with OUD.

Baseline covariates.—We considered numerous baseline covariates, measured across all three harmonized trials, that could potentially act as confounders and/or effect modifiers, many of which were used in previous analyses,[36,41] listed in Table 1. We note that we use SuperLearner in model fitting (discussed below), and this data-adaptive modeling approach will incorporate these baseline covariates as confounders as well as effect modifiers when such effect modifier incorporation improves model t. Baseline covariates included study site (unique across trials), race/ethnicity (non-Hispanic/Latinx white, non-Hispanic/Latinx black, Hispanic/Latinx, other (including multiracial)), age (years), sex (male, female), highest level of past opioid withdrawal discomfort (none, mild, moderate, severe), past-year substance use disorders: alcohol use disorder, cocaine use disorder; history of neurological injury, epilepsy diagnosis, history of psychiatric disorders: schizophrenia, bipolar, anxiety or panic disorder, major depressive disorder; history of IV drug use; and past 30-day drug use: amphetamines, cannabis, and benzodiazepines.

Time-varying covariates.—We considered the time-varying covariates of 1) most recently prescribed dose and 2) weekly illicit opioid use that was under the threshold of what was considered relapse. Missing BUP-NX dose was carried forward from the previous week (methdone dose had no missingness). Weekly illicit opioid use was assessed weekly, and was positive if the participant's urine drug screen was positive or if the participant reported illicit opioid use in the Timeline Followback interview or if it was missing. Urine drug screens at weeks 1 and 2 could have been affected by medication used for medically managed withdrawal, so for these weeks we did not use drug screen data.

Statistical analysis.

Using weekly data, we modeled the longitudinal relationship between the time-varying exposure of dose *increase* on risk of relapse during the subsequent week, conditional on the previous week's opioid use and dose (time-varying covariates), and baseline covariates. This longitudinal modeling approach uses sequential regression[42–44] such that the most recently prescribed dose and previous week's opioid use influence the likelihood of having a dose increase, which then affects the dose administered and likelihood of subsequent

opioid use in a reciprocal manner.[45,46] We include a directed acyclic graph depicting the longitudinal data structure and denoting the relationships that contribute to the longitudinal effect estimates in Figure A1 in the appendix. We then used this model to predict risk of relapse under four treatment strategies:

1. *Dynamic dose increase*, d1: If, every time there was opioid use, dose was subsequently increased (by any amount), up to the allowable maximum (32mg for BUP-NX, and the observed maximum of 397mg for methadone).
2. *Increase dose to threshold*, d2: If dose was increased (by any amount) every week until a minimum threshold of 16mg for BUP-NX or 100mg for methadone was reached. These thresholds were chosen based on prior research[15,16,47–49] and the median maximum daily dose values in the data.
3. *Threshold and dynamic dose increase*, d3: A hybrid strategy, where dose was increased every week until a minimum threshold of 16mg for BUP-NX or 100mg for methadone was reached, and then increased every time there was opioid use thereafter. This is a combination of the previous two treatment scenarios.
4. *Constant dose*, d4: If dose remained constant after the third week of treatment, regardless of use.

We use t to denote week of treatment, and $t = 0$ denotes randomization. Let $A_t = 1$ denote increased dose at week t for $t \in \{2, 3, \ldots, 11\}$. Let L_t denote the time-varying covariates at week t. We estimated the effect of a dosing strategy, $d(L_{t-1})$, in which dose increase at week t would be assigned according to the values of the time-varying covariates L_{t-1} for $t \in \{2, 3, \ldots, 11\}$. Specifically, $d(L_{t-1}) = 1$ denotes increased dose at week t in response to the values L_{t-1}. We define each of the above strategies in terms of this notation in the Appendix.

The time-varying covariate of opioid use was missing for 13.2%–17.7% of BUP-NX patients, depending on week, and for 12.6%–17.8% of methadone patients. However, missed visits or refused urine samples were considered positive for opioid use (discussed above), resulting in functionally no missingness for this variable or for the outcome. The time-varying covariate of buprenorphine dose was missing for between 0.1% and 2.6% of uncensored participants, depending on the timepoint (where uncensored at time t means those who had not yet relapsed and were still participating in the study at time t). Methadone dose was not missing for any participants. For missing BUP-NX dose, we carried forward the previous dose, which we believe it is more accurate than imputing, because the last prescribed dose is what the participant would have access to through the trial. Baseline covariate missingness was minimal (≤ 4%), however to preserve use of the full sample, we imputed the few missing observations using chained equations, resulting in five imputed datasets.[50] This approach assumes that data are missing at random conditional on the variables in the imputation model. We combined the resulting estimates across imputed datasets using Rubin's combining rules.[51]

We estimated the average treatment effect: $P(Y_d \leq t) - P(Y_{d4} \leq t)$ for all $t \in \{3, \ldots, 12\}$, where Y_d denotes the counterfactual risk of relapse in a hypothetical world where dose would be increased according to $d \in \{d1, d2, d3\}$. In words, $P(Y_d \leq t) - P(Y_{d4} \leq t)$, is the

expected risk of relapse by time t contrasted under the longitudinal, counterfactual dosing strategy d (representing one of the three dosing strategies above) versus the reference of constant dose. We also estimated the average treatment effect: $P(Y_{d3} \leq t) - P(Y_d^* \leq t)$ for all $t \in \{3, \ldots, 12\}$, where Y_{d3} denotes the counterfactual risk of relapse in a hypothetical world where dose would be increased according to the hybrid strategy, and where Y_d^* denotes the counterfactual risk of relapse in a hypothetical world where dose would be increased according to strategy $d^* \in \{d1, d2\}$. In other words, this compares the hybrid dosing strategy to each of its components.

We present estimates of: 1) the difference in predicted risk of relapse under each of the dosing strategies d1, d2, and d3 versus under constant dose ($P(Y_d \leq t) - P(Y_{d4} \leq t)$), which is called the additive treatment effect (ATE), risk difference (RD), or the treatment effect on the additive scale; 2) the ratio of predicted risks of relapse under each of the dosing strategies d1, d2, and d3 relative to the predicted risk under constant dose (denoted $\frac{P(Y_d \leq t)}{P(Y_{d4} \leq t)}$), which is called the relative risk (RR) or the treatment effect on the relative scale; 3) the difference in predicted risk of relapse under dosing strategy d3 versus strategy d1 or versus strategy d2 ($P(Y_{d3} \leq t) - P(Y_d^* \leq t)$); and 4) the ratio of predicted risks of relapse under dosing strategy d3 relative to the predicted risk under each of the strategies d1 and d $\left(\frac{P(Y_{d3} \leq t)}{P(Y_{d^*} \leq t)}\right)$

We used a longitudinal sequentially doubly robust estimator to estimate the above effects,[33] and incorporated an ensemble of machine learning algorithms[52] to flexibly model relationships (an intercept-only model, a main-effects generalized linear model, LASSO[53], multivariate adaptive regression splines (MARS),[54] and light gradient boosting machine (LightGBM)[55]). We chose these algorithms because they each represent a different general family of algorithms: generalized linear models, trees (LightGBM), and splines (MARS). Variances were estimated using the sample variance of the influence curve.[33] Note that individuals were considered no longer at-risk for the outcome after their first relapse event. We assessed the extent to which there was evidence of practical violations of the positivity assumption by examining the maximum density ratio that was part of the weights in the sequentially doubly robust estimator for each medication, dosing strategy, and treatment week. We did not find evidence of such violations (Table A5 of the appendix).

We used R (version 4.2.1) for all analyses[56] with the lmtp[57,58] and SuperLearner packages.[59] Code to replicate the analyses is available https://github.com/kin-epici/OUD-dynamic-dosing

Results

Table 1 displays descriptive information on the participants initiating treatment with BUP-NX or methadone across the three trials. This table is further subdivided into those who never used illicit opioids during weeks 2–11 of treatment (“never used”), those who ever used illicit opioids during this time period (used”), those who never had their dosage increased during weeks 2–11 of treatment (never increased”), and those who ever had their dosage increased during weeks 2–11 (“increased”).

Table 2 gives the number of participants who were observed to follow each treatment strategy by week (rows labeled Total). In addition, among those who followed a particular treatment strategy, Table 2 breaks down those who received an increase under the treatment strategy vs. not. We see ample variation across strategies and across weeks among those treated with methadone. Among those treated with BUP-NX, many individuals receive dose increases under d1 early in treatment, but fewer later in treatment. This is largely because as individuals continue in BUP-NX treatment, they are less likely to use opioids. For d2, we again see many individuals receiving dose increases under this strategy early in treatment, but fewer later in treatment, because as individuals continue in BUP-NX treatment, they are less likely to be on doses <16mg. We see a similar pattern for d3, though note that numbers receiving a BUP-NX dose increase in later weeks is slightly larger. Many participants fall under the constant dosing strategy, d4, at each week. However, for many of these individuals, ranging from 64% to 90%, depending on week, dose increases would have been indicated (but did not occur) applying either the minimum threshold criteria or the recent use criteria (row labeled "$d3^{C}$"under d4). We note that there were also a substantial number of participants whose dose was increased in the absence of use, as shown in Table A3 in the appendix.

Figure 1a shows the estimated cumulative risk of relapse by week for each of the four dosing strategies among those treated with BUP-NX. Figure 1a also shows the differences in risks of relapse (risk differences, RD) comparing each of the dosing strategies $d \in \{d1, d2, d3\}$ to the reference of constant dose (d4), along with their associated 95% confidence intervals (CIs) at each week, again among those treated with BUP-NX. We see that each of the BUP-NX dosing strategies involving dose increases reduces risk of relapse at each week after week 3, as compared to keeping dose constant, but more so earlier in treatment. This reduction is statistically significant at all weeks for strategies d2 and d3 and at weeks 4–7 for strategy d1. For example, the hybrid strategy for increasing BUP-NX dose would reduce risk of relapse by week 12 by 13% (RR: 0.87, 95% CI: 0.80, 0.95) as compared to holding dose constant, translating to a number needed to treat (NNT) of 14.

Figure 1b shows the estimated cumulative risk of relapse by week for each of the four dosing strategies among those treated with methadone. The estimates generally have wider confidence intervals for methadone than for BUP-NX. We see evidence that strategies involving dose increases significantly reduce risk of relapse across weeks. For example, the hybrid strategy for increasing methadone dose would reduce risk of relapse by week 12 by 20% (RR: 0.80, 95% CI: 0.71, 0.90) as compared to holding dose constant after week 3, translating to an NNT of 8.

Table A1 in the appendix provides the point estimates and 95% CIs for each contrast for BUP-NX and for methadone.

We also compared the effect of d3 to each of its components (d1 and d2). Table A2 in the appendix provides the point estimates and 95% CIs for each of these contrasts for BUP-NX and methadone. For BUP-NX, d3 would reduce risk of relapse at each week, as compared to d1 or d2 (Table A2). For methadone, d3 performed similarly to d1 and d2.

Discussion

We found that a strategy in which dose would be increased weekly until a threshold (16mg for BUP-NX, 100mg for methadone) is reached or a strategy in which dose would be increased in response to opioid use were each estimated to reduce risk of relapse over 12 weeks of treatment. A hybrid dosing strategy that combined these components performed better than either component alone for BUP-NX treatment. The hybrid strategy performed similarly to either strategy alone for methadone treatment. The degree to which dynamic dosing strategies d1 – d3 reduced risk as compared to the constant dose strategy appeared to level off around week 6 (Figure 1 and Table A1). This could, in part, be because: 1) the number of participants meeting the threshold dose levels off around week 6, and 2) that the number of participants with prior with use also levels off around week 6 (see Table A4 in the appendix). It could also be because different strategies may either be working or not within the first few weeks of treatment, though this is speculative.

Our findings are aligned with current clinical consensus opinion on dosing strategies for BUP-NX and methadone treatment for OUD,[14] as summarized in the Introduction. However, to our knowledge, the current study, along with a previous study,[28] provides some of the first evidence *quantifying* the effects of these dosing strategies on OUD-related outcomes. The previous study found that increase BUP-NX dose in response to use would significantly reduce risk of relapse to OUD over 24 weeks of treatment.[28] The present study corroborates this earlier work. It also builds on it by: 1) using secondary data from three trials instead of just one, thus greatly increasing sample size; 2) estimating effects of other dosing strategies, including increasing dose to a minimum threshold and the hybrid strategy; and 3) estimating the effects of dosing strategies for methadone.

Strengths and Limitations.

Our utilization of weekly data up to 12 weeks of treatment from three large, harmonized multi-site clinical trials for the treatment of OUD are strengths, providing a large sample size with enough naturalistic variation in dosing to contrast dosing strategies. However, the three trials were neither designed nor powered to test the effect of dynamic, individualized treatment strategies on risk of relapse. Although combining data across trials resulted in a relatively large sample size, there were nonetheless treatment strategies that were observed for a small number of participants (Table 2). In particular, we observed few participants with BUP-NX increases each week after week 6, which means that our conclusions regarding the benefits of dose increases after week 6 should be treated with caution.

The trials also enrolled disparate patient populations, though we controlled for study site, which was unique across trials.[23,34–36] The effects we estimated were allowed to vary across trials and trial sites, and the resulting estimates were overall averages, which may differ from trial or site-specific effects. Although we lack the cell sizes to stratify the BUP-NX analysis by trial (Table A6 in the appendix), we include stratified analyses through week 6 in Figures A3–A5 in the appendix. Analogously, our effect estimates may not generalize to other OUD treatment-seeking populations.

Another limitation was that this was an observational analysis, so our results may have been biased due to residual confounding due to unmeasured variables (e.g., patient motivation). We addressed confounding due to measured variables in several ways. We incorporated numerous baseline covariates. We used a sequentially doubly robust estimator of longitudinal effects,[33] which means that our estimates are expected to be unbiased even if either the treatment model or outcome model are consistently estimated at each timepoint. Additionally, the estimator appropriately adjusted for time-varying confounders of non-study opioid use and dose and the time-varying exposure of dose increase.[33] Lastly, we used an ensemble of machine learning algorithms to flexibly fit each model and 10-fold cross validation to mitigate risk of over tting.[52]

In addition, it is possible that there is not a single best dosing strategy for all patients. It is plausible that the best strategy could be subgroup-specific, depending on a patient's clinical and/or demographic characteristics, and may even vary over time as those characteristics change. We are currently working on learning such a time-varying, individualized dynamic optimal treatment rule for when doses should be increased, and as such, it is the topic of a future paper.

Conclusions.

Future research should test the effect of dynamic dosing strategies experimentally with prospective randomized trials, comparing fixed or usual treatment strategies to strategies that increase dose to a threshold and further increase dose in response to ongoing opioid use. Our findings support the clinical recommendation, also partially reflected in current guidelines,[14] that, doses be targeted toward minimum thresholds and, in the case of BUP-NX, that doses be raised when patients continue to use opioids.

Highlights

- We sought to answer the question: Among those initiating buprenorphine-naloxone or methadone treatment for opioid use disorder, what dosing strategy would result in the lowest risk of relapse in the first 12 weeks of treatment?
- We found that doses should be targeted toward minimum thresholds and, in the case of buprenorphine, raised when patients continue to use opioids.
- For buprenorphine, 1) increasing dose in response to opioid use or 2) increasing dose to a minimum of 16 mg and subsequently increasing in response to use, both resulted in the lowest risk of relapse.
- For methadone, holding dose constant resulted in greatest risk of relapse; the other three strategies of 1) increasing dose until a minimum threshold of 100mg was reached, 2) increasing dose in response to use, or 3) increasing until the minimum threshold and subsequently increasing in response to use performed similarly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

This work was supported by the National Institute on Drug Abuse (R00DA042127; PI Rudolph) and the Data Science Institute (PI Rudolph, Co-I Luo).

Sources of financial support:

This work was supported by the National Institute on Drug Abuse (R00DA042127; PI Rudolph) and the Columbia University Data Science Institute (Rudolph, Luo).

Conflicts of interest:

JR has received medication and/or other support for research studies from Alkermes, Reckitt-Benckiser, Indivior, and Braeburn. EVN has received medication for research studies from Alkermes/ Cephalon, Duramed Pharmaceuticals, and Reckitt-Benckiser. MF has been a consultant for Alkermes, Drug Delivery LLC, and has received research support from Alkermes. The remaining authors have no conflicts of interest to report.

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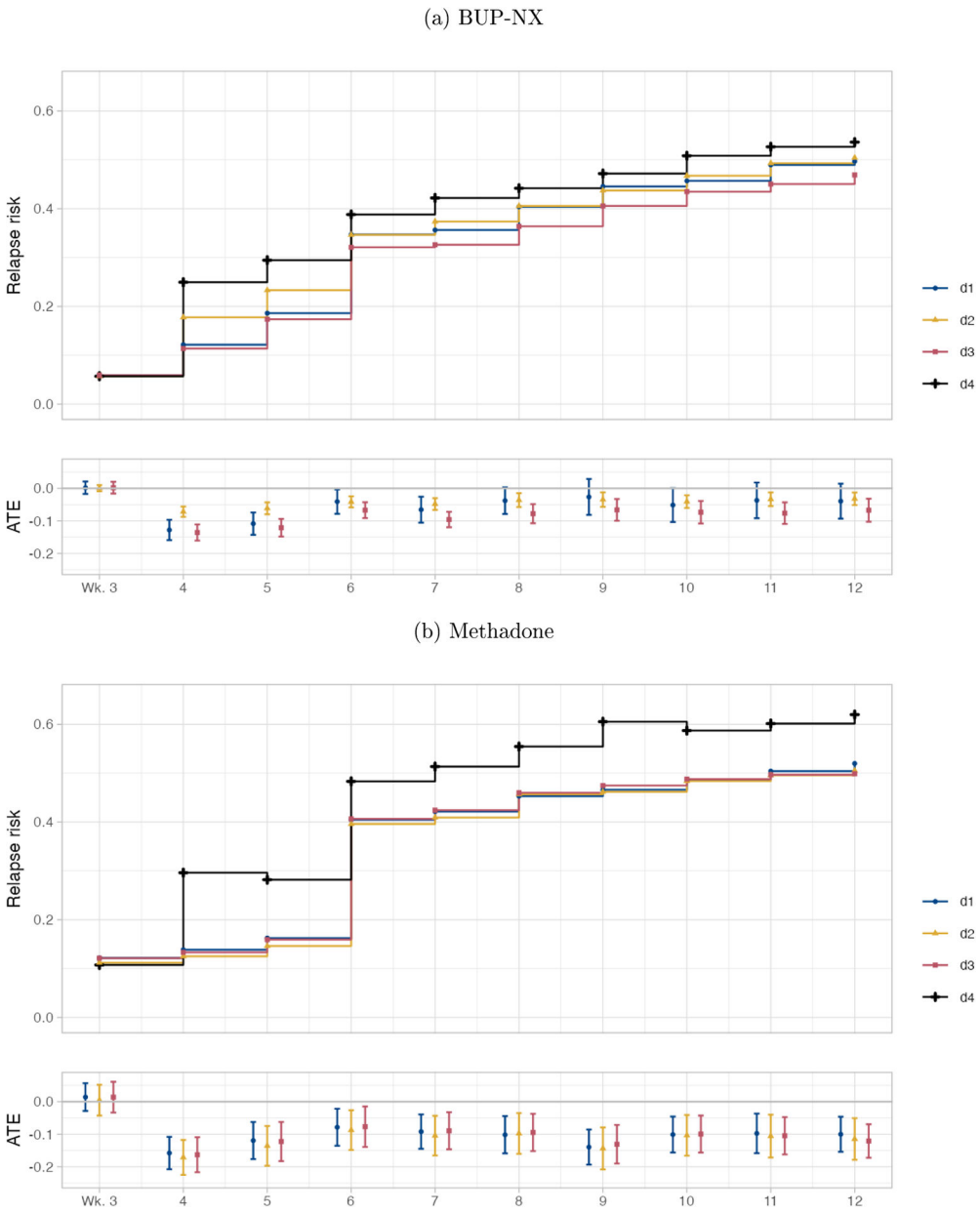

Figure 1:

Estimated marginal risks of relapse and average treatment effects (with 95% confidence intervals), comparing dosing strategies d ∈ {d1, d2, d3} to the reference of constant dose (d4), among (a) patients randomized to BUP-NX and (b) patients randomized to methadone.

Table 1:

Descriptive statistics for those initiating treatment with BUP-NX or methadone

	All	Never used	Used	Never increased	Increased
BUP-NX	**N = 1348**	**318**	**1030**	**771**	**577**
Trial					
CTN0027	53.3%	33.0%	59.5%	55.1%	50.8%
CTN0030	26.7%	28.6%	26.1%	29.4%	23.1%
CTN0051	20.0%	38.4%	14.4%	15.4%	26.2%
Age	34.92 (10.72)	35.62 (10.74)	34.71 (10.72)	34.39 (10.54)	35.64 (10.93)
Women	33.8%	35.2%	33.3%	33.3%	34.3%
Race/ethnicity					
Non-Hispanic white	72.0%	78.9%	69.9%	74.6%	68.6%
Non-Hispanic Black	6.8%	4.4%	7.6%	5.1%	9.2%
Hispanic	14.2%	11.3%	15.1%	12.3%	16.8%
Other (including multiracial)	6.9%	5.3%	7.4%	8.0%	5.4%
Current IV drug use	51.4%	44.2%	53.5%	50.7%	52.3%
Current cannabis use	36.1%	36.2%	36.1%	35.7%	36.6%
Current amphetamine use	12.8%	11.9%	13.0%	11.9%	13.9%
Current benzodiazepine drug use	23.8%	24.5%	23.6%	23.8%	13.9%
Alcohol use disorder	19.6%	23.1%	18.5%	16.9%	23.2%
Cocaine use disorder	25.6%	26.9%	25.2%	25.4%	25.9%
Neurological injury	12.0%	13.2%	11.7%	10.3%	14.4%
History of epilepsy	4.8%	6.3%	4.4%	3.4%	6.8%
History of schizophrenia	1.6%	0.9%	1.8%	2.0%	1.0%
History of bipolar disorder	10.7%	10.7%	10.7%	9.5%	12.3%
History of anxiety disorder	33.8%	35.5%	33.3%	31.1%	37.4%
Opioid withdrawl discomfort (1–4)	2.58 (0.66)	2.66 (0.74)	2.55 (0.64)	2.54 (0.62)	2.62 (0.72)
Max dose (mg) [median]	19.54 (7.60)	18.81 (6.95)	19.77 (7.78)	17.99 (7.92)	21.61 (6.61)
Max dose (mg) [IQR]	16.00, 24.00	14.00, 24.00	16.00, 24.00	12.00, 24.00	16.00, 24.00
No. dose increases	0.62 (0.85)	0.68 (0.90)	0.60 (0.83)	0.00 (0.00)	1.44 (0.71)
Week of relapse	9.29 (3.95)	11.73 (2.79)	8.54 (3.96)	8.68 (4.13)	10.12 (3.54)
Relapse by week 12	52.2%	20.1%	62.0%	57.2%	45.4%
Methadone	**N = 515**	**75**	**440**	**87**	**428**
Age	36.93 (10.92)	35.39 (10.86)	37.19 (10.92)	38.03 (11.00)	36.70 (10.90)
Women	32.6%	42.7%	30.9%	32.2%	32.7%
Race/ethnicity					
Non-Hispanic white	68.9%	80.0%	67.0%	59.8%	70.8%
Non-Hispanic Black	8.7%	5.3%	9.3%	12.6%	7.9%
Hispanic	15.5%	12.0%	16.1%	17.2%	15.2%
Other (including multiracial)	6.8%	2.7%	7.5%	10.3%	6.1%
Current IV drug use	70.8%	44.0%	75.4%	76.7%	69.6%
Current cannabis use	27.6%	34.7%	26.4%	29.1%	27.3%

	All	Never used	Used	Never increased	Increased
Current amphetamine use	13.4%	6.7%	14.6%	18.6%	12.4%
Current benzodiazepine drug use	15.6%	12.0%	16.2%	11.6%	12.4%
Alcohol use disorder	22.0%	24.3%	21.5%	14.1%	23.6%
Cocaine use disorder	33.1%	27.0%	34.2%	36.5%	32.5%
Neurological injury	9.3%	9.3%	9.3%	4.6%	10.3%
History of epilepsy	1.9%	1.3%	2.0%	4.6%	1.4%
History of schizophrenia	2.1%	0.0%	2.5%	3.4%	1.9%
History of bipolar disorder	12.1%	12.0%	12.1%	12.6%	11.9%
History of anxiety disorder	31.1%	29.3%	31.4%	19.5%	33.5%
Opioid withdrawl discomfort (1–4)	2.45 (0.57)	2.50 (0.60)	2.44 (0.57)	2.44 (0.64)	2.45 (0.56)
Max dose (mg)	78.94 (33.73)	86.16 (48.27)	77.71 (30.48)	44.34 (15.57)	85.97 (32.06)
Max dose (mg) [IQR]	57.50, 100.00	53.50, 102.50	60.00, 95.00	37.50, 50.00	65.00, 100.00
No. dose increases	2.33 (1.92)	3.11 (2.17)	2.20 (1.85)	0.00 (0.00)	2.81 (1.77)
Week of relapse	8.90 (4.00)	12.04 (2.51)	8.37 (3.96)	6.47 (3.82)	9.40 (3.86)
Relapse by week 12	56.1%	14.7%	63.2%	79.3%	51.4%

Table 2:

Number of patients randomized to receive BUP-NX and methadone that were observed as following a given strategy: (1) increased dose under the strategy and were observed as increasing dose, or (0) had a constant dose under the strategy and were observed as having a constant dose.

	Wk. 2	3	4	5	6	7	8	9	10	11
Constant dose strategy, d4										
BUP-NX										
d1[a]	375	269	227	125	115	107	112	89	75	78
d2[b]	316	258	235	200	192	191	174	162	161	155
d3[c]	557	444	396	295	281	269	255	230	220	214
Total	1028	1109	947	928	801	779	748	710	675	647
Methadone										
d1[a]	88	93	115	46	50	45	41	37	40	31
d2[b]	158	186	221	168	168	164	145	139	125	118
d3[c]	160	187	229	176	176	173	154	150	139	129
Total	182	223	253	270	220	216	205	211	198	189
Increase dose in response to use strategy, d1										
BUP-NX										
Increase	147	59	40	24	11	6	7	4	4	3
Constant	605	702	685	698	661	652	614	602	589	560
Total	752	761	725	722	672	658	621	606	593	563
Methadone										
Increase	216	133	83	64	16	16	13	12	12	14
Constant	72	100	128	157	158	165	157	169	154	153
Total	288	233	211	221	174	181	170	181	166	167
Increase dose if under threshold strategy, d2										
BUP-NX										
Increase	67	26	21	13	9	3	6	3	3	4
Constant	695	770	696	699	597	584	561	536	510	490
Total	762	796	717	712	606	587	567	539	513	494
Methadone										
Increase	312	200	122	89	43	33	30	18	20	14
Constant	2	5	22	34	41	45	52	64	69	64
Total	314	205	144	123	84	78	82	82	89	78
Hybrid dosing strategy, d3										
BUP-NX										
Increase	182	72	55	34	18	9	12	7	6	6
Constant	423	511	513	527	492	488	465	457	443	424
Total	605	583	568	561	510	497	477	464	449	430
Methadone										

	Wk. 2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Increase	325	215	136	106	51	38	35	22	27	24
Constant	0	4	12	23	31	35	42	53	54	52
Total	325	219	148	129	82	73	77	75	81	76

[a]No. of dose increases that would have been indicated applying d1

[b]No. of dose increases that would have been indicated applying d2

[c]No. of dose increases that would have been indicated applying d3