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A Novel Assessment of Longitudinal Buprenorphine Dose: Defining the "Optimal" Dose.

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Background

Buprenorphine, a mu-opioid partial agonist, has been clinically indicated as a first-line medication-assisted treatment for opioid use disorder (OUD) since its FDA approval in 2002. Additionally, the FDA has approved Suboxone®, a sublingual buprenorphine/naloxone product, designed to reduce the possibility of diversion of buprenorphine. The naloxone has no effect when taken sublingually; but if the sublingual tablet is crushed and used parenterally it sends the person into withdrawal, so it won't be abused this way.

Buprenorphine's less stigmatized clinician office-based treatment and less highly regulated designation when compared to other common treatments such as methadone, a mu-opioid full agonist, is making buprenorphine surge in popularity. However, many clinicians are left without guidance on effective dosing practices resulting in considerable variability in prescribing practices, which undoubtedly affects patient adherence in treatment. Research has been done into time-weighted average daily buprenorphine dosages (Bergen et al, 2022) among patients enrolled in several NIDA clinical trials, of which publicly shared data is available. These data have yet to be analyzed for demographic differences in buprenorphine dose.

We have not found previously published literature defining optimal buprenorphine dose, and much of the literature on buprenorphine dosage does not examine differences amongst demographic groups such as race and sex. We examine these data to assess how effective 'optimal' buprenorphine dose may differ among different demographic groups.

Methods

Our project examines the data from the NIDA Buprenorphine Clinical Trials, of which there are 13 when searching the word 'buprenorphine' in the NIDA Data Share database. Of the 13, we examined three studies aimed to examine buprenorphine's potential in decreasing illicit use of opioids, had sufficient sample sizes, and authorized physicians to vary in their prescribing of buprenorphine. All 3 trials had patient-level data released which included buprenorphine dosing, demographics, and urine toxicology results. The trials are listed below in Table 1.

Table 1: Descriptions of Examined NIDA Randomized Clinical Trial (RCTs)

Trial Name	Years Conducted	Description	# Screened Individuals
CSP-1008A : A Multicenter Efficacy/Safety Trial of Buprenorphine/Naloxone for the Treatment of Opiate Dependence	1996-1997	Phase 1: 4-week randomized double-blind efficacy trial using three treatment categories: BUP/BUP-NX/Placebo. Phase 2: 48-week randomized open-label safety trial using two treatment categories: BUP/BUP-NX	N=449
CSP-1008B: A Multicenter Safety Trial of Buprenorphine/Naloxone for the Treatment of Opiate Dependence	1996-1997	52 week randomized open label safety trial using BUP-NX	N=282
CTN-0027: Starting Treatment with Agonist Replacement Therapies (START) Study	2006-2010	24-32 week randomized trial on effects of BUP-NX vs. Methadone for liver health	N=1920

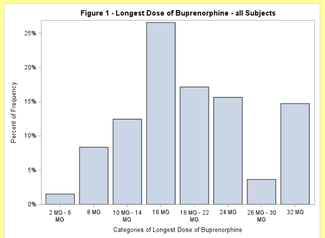
To assess what might be the optimal dose of buprenorphine to inhibit use of non-prescribed opioids and the efficacy of that dose in preventing relapse, we examined both the dose prescribed for the longest period of time (which we here denote the longest dose) and the maximum dose. Our own unpublished preliminary data on methadone suggests that the longest dose is optimal. All clinical trials stipulated that the maximum dose of buprenorphine could not surpass 32 mg per day. Only patients classified by the clinical trial to have tested negative for opiates throughout their duration in the trial were examined further.

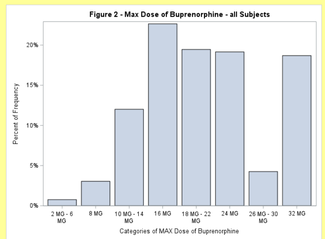
Patients were classified by biological sex and self-reported racial/ethnic group. Only white non-Hispanic (**WNH**), black non-Hispanic (**BNH**), and Hispanic patients were analyzed due to the low number of patients in other racial/ethnic categories.

Results

Of the 2651 total screened patients, 1150 patients prescribed buprenorphine had completed the trials successfully. 612 patients tested negative for opiates in urine throughout their duration of the trial. 15.1% (N=90) identify as BNH, 13.4% (N=80) identify as Hispanic, and 71.5% (N=426) identify as WNH. We excluded N=19 patients from analysis who self-identified as "Other" race. 30.4% (N=181) of the patients are female and 69.6% are (N=415) male.

Of those whose urine tested negative for opiates throughout the entire trial, the mean longest dose was 19.70mg and mean max dose was 21.30mg. Of those who ever had positive urine test, the average longest dose was 18.63mg and average max dose was 19.71mg. The longest and maximum dose of buprenorphine were significantly higher among patients who always had negative urine screens than among those who ever had a positive urine test ($p<0.001$ for longest dose, $p<0.05$ for maximum dose). Figures 1 & 2 examine the distribution of longest and max dose, respectively, among **all patients who tested negative for opiates** throughout the trial.



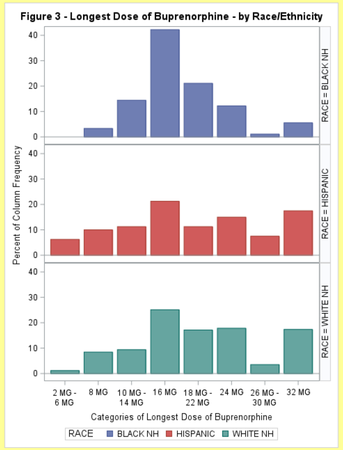


Analyzing dose magnitude, BNH subjects had significantly lower longest ($p=0.0013$) and max doses ($p<0.001$) compared to their WNH counterparts (two-tailed t-tests). When comparing the difference in magnitude of dosing between BNH and Hispanics, BNH subjects had a significantly lower max dose ($p<0.01$), but there was no significant difference when comparing longest dose. There is no significant difference in magnitude for either maximum or longest dose when comparing WNH and Hispanics. Table 2 displays summary statistics stratified by race/ethnicity.

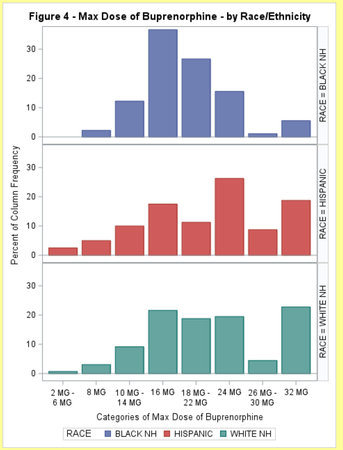
Table 2: Descriptive Analysis of Dosing Variables stratified by Race

RACE	Variable	N	Mean	Minimum	Lower Quartile	Median	Upper Quartile	Maximum
BLACK NH	Longest Dose	90	17.93	8.00	16.00	16.00	20.00	32.00
	Max Dose	90	18.64	8.00	16.00	16.00	20.00	32.00
HISPANIC	Longest Dose	80	19.38	2.00	13.00	20.00	25.00	32.00
	Max Dose	80	21.49	2.00	16.00	24.00	27.50	32.00
WHITE NH	Longest Dose	426	20.13	4.00	16.00	20.00	24.00	32.00
	Max Dose	426	21.81	6.00	16.00	20.00	28.00	32.00

When examining differences in the distribution of both longest and max buprenorphine dose by racial/ethnic groups, WNH and BNH had significant differences in the variance for both max ($p=0.0004$, folded F-test) and longest ($p=0.0003$), as illustrated by the difference in the shape of the distributions below. Likewise, there is a similar difference between BNH and Hispanics with respect to both maximum dose ($p=0.0006$) and longest dose ($p<0.0001$). However, the distributions of longest and maximum dose among WNH and Hispanics, are quite similar ($p=0.075$).

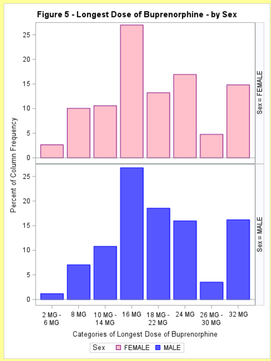


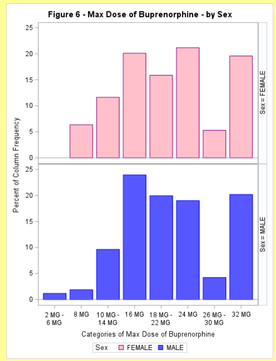
Distributions of longest and maximum buprenorphine dose are noted below in Figures 3 and 4, respectively.



Results (continued)

Distributions of both longest dose and max dose were similar between the sexes, as shown in Figures 5 and 6, with no significant differences in either magnitude or variability. Considering dose magnitude for females, the mean longest dose was 19.38mg and mean max dose was 21.18mg. For males, the mean longest dose was 19.83mg and the mean maximum dose was 21.33mg.





Conclusions

Based on our results we can conclude the following:

1. Those patients with successful treatment outcome, quantified as the absence of positive urine test for non-treatment opiates, have a statistically significant higher max and longest daily buprenorphine dose than those with the presence of positive opiate urine tests throughout treatment.
2. BNH patients are treated on average with lower longest buprenorphine dosages when compared to WNH & Hispanic counterparts; however, this magnitude is only significant between BNH & WNH.
3. WNH & Hispanics do not differ significantly in magnitude or variability of max and longest daily buprenorphine dosages for treatment of OUD.
4. There is no significant difference in magnitude or variability of mean max and longest daily dosing when comparing sex.

Limitations to our Results:

1. Our study sample has limited numbers of Hispanic and BNH patients compared to WNH patients. The lack of equal racial representation in the study sample could be due to a multiplicity of factors stemming from social, cultural, and medical reasons.

Future Directions

Our finding of significant difference in optimal daily buprenorphine dosing among demographic groups poses for future research questions to explain this difference. Genomic studies of those undergoing buprenorphine treatment for OUD could provide greater insight into possible differences of genetic variants that affect optimal buprenorphine dosage. Different treatment approaches by clinicians with serving different mixes of demographic groups could be another factor affecting such variability in dosing. Ultimately, these and other studies may provide guidance to clinicians using buprenorphine to treat persons with OUD to create individualized dosing protocols, starting patients on better approximations of their optimal dosage, and thus minimizing the additional time it takes in adjusting daily buprenorphine dosage to achieve its therapeutic effect.

Citations

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The information reported here results from secondary analyses of data from clinical trials conducted by the National Institute on Drug Abuse (NIDA). Specifically, data from the following trials were included: CSP-1008A, "A Multicenter Efficacy/Safety Trial of Buprenorphine/Naloxone for the Treatment of Opiate Dependence"; CSP-1008B, "A Multicenter Safety Trial of Buprenorphine/Naloxone for the Treatment of Opiate Dependence"; and, CTN-0027, "Starting Treatment with Agonist Replacement Therapies (START)"

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