Opioid Relapse Prevention: A Survival Analysis Comparing Two Treatments Adjusting for Covariates

Abstract

Existing research proves that extended-release naltrexone (XR-NTX) and buprenorphine-naloxone (BUP-NX) are effective treatments in preventing opioid relapse; however, identifying covariates important in survival outcomes remains yet to be done. Our study fills in these gaps and provides a sturdier analysis comparing these two treatments and the safety of the treatments as it is related to adverse events. We used data from a study sponsored by the NIDA Clinical Trials Network to develop our models and draw our conclusions (1). Our methodology consisted of survival analysis techniques such as Cox Proportional Hazard modeling and log-rank tests. The results show that patients in the intention to treat population receiving BUP-NX have a significantly longer relapse-free time than those receiving XR-NTX. Also, we found that covariates including race, mental health history, opioid cravings, and even the presence of a skin condition played significant roles in determining the likelihood of relapse.

Background and Significance

The widespread misuse of opioids across the United States has created significant economic and social repercussions, with the total cost associated with the opioid epidemic estimated to be $78.5 billion in 2013 (2). With increased prescription of opioids as treatment for chronic pain in recent years, the rate of prescription overdose deaths has also risen (3). Effective treatments for opioid addiction are thus of great interest.

We seek to compare the safety and efficacy of two pharmacological detoxification treatments for opioid relapse: extended release naltrexone (XR-NTX) and buprenorphine-naloxone (BUP-NX). Additionally, we seek to analyze underlying covariates in patient profiles that may contribute to time to relapse. Our primary outcome of interest is relapse free survival time, with relapse defined as 4 consecutive weeks of opioid use detected by urine toxicology or self-report, or 7 consecutive days of self-reported use (1). Furthermore, in the trial, censoring of patients occurred at 24 weeks. Existing literature on the abuse of other substances have examined mood and anxiety disorders, outcome expectations, cravings and urges, and situational/environmental factors (4). Thus, we hypothesize that variables related to a patient's mental health, motivation for participation in the study, race, cravings for opioids and other substances, and family and social relationships have a statistically significant impact on time to relapse.

Methods

Data Collection Our data originates from a randomized controlled 24 week study spanning various start dates between 2014 and 2016 titled "Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial" comparing the effectiveness of XR-NTX versus BUP-NX for opioid relapse (1). According to the study, "participants were 18 years or older, had Diagnostic and Statistical Manual of Mental Disorders-5 opioid use disorder, and had used non-prescribed opioids in the past 30 days" (1). The data consisted of 65 datasets detailing information pertaining to which drug the patient received, date of study completion or last visit, and reason for ending participation in the study–among other information like demographics and health measures.

Variable Creation If a variable seemed useful in comparing XR-NTX and BUP-NX, it was added into a larger dataset. This was done by determining if a dataset had variables that are generally associated with worse health outcomes. For example, the misuse of other prescription drugs is generally associated with worse health outcomes. Once we narrowed down our initial list to 15 datasets, we merged them all into one larger dataset and filtered for the variables that we planned to concentrate on in our analysis. After looking at datasets pertaining to demographics, substance use disorder, cravings, preferred treatment, family and social relationships,tobacco use, and several other topics of interest, we used log-rank tests within those datasets to determine which variables were statistically significant. A list of relevant variables and their descriptions can be found in Tables 2 and 3.

Analytic Methods To compare the efficacy of both treatments against relapse and assess the statistical significance of the covariates we identified, we constructed a Cox Proportional Hazards Model and a Kaplan-Meier Curve using the *survival* package in R (5). In order to get the final list of parameters that is the best fit for our Cox model, we used stepwise variable selection using the *My.Stepwise* package in R (6). To compare the safety of both drugs, we conducted a two-proportion Z-test on adverse events thought to be associated with each drug. We treated samples as independent for the purposes of this test and assumed that our sample was sufficiently large ($n>30$). For this test, we used the AD1 dataset as published by the authors of the study (1). Our predetermined significance level was α=0.05.

Results

For the intention to treat group, the Kaplan-Meier curve illustrates a stark difference between the XR-NTX treatment and the BUP-NX treatment. The XR-NTX curve is always below the BUP-NX curve after 44 days, with little to no overlap in the 95 percent confidence intervals (see Figure 1). In order to formally conclude that there is a significant difference between the survival probability of the two groups, we conducted a log-rank test. When only testing between the two treatment groups, we found the chi-squared test statistic to be 10.1 on 1 degree of freedom ($p<0.05$). Thus, we have sufficient evidence to reject the null hypothesis that the relapse free survival time is the same between the two groups.

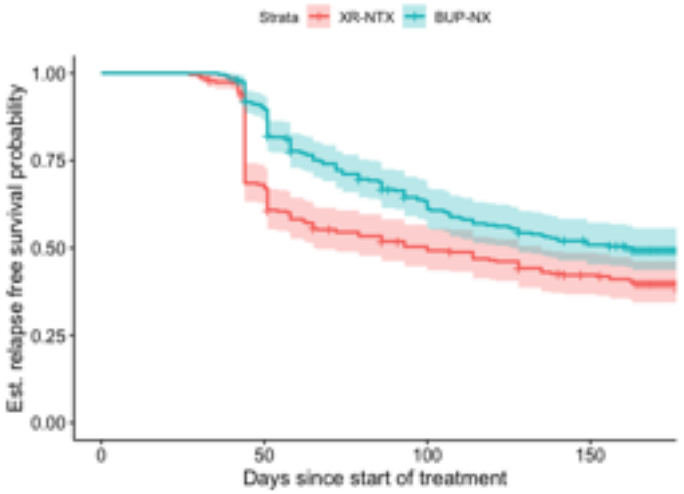

Figure 1: Relapse-free survival over time for intention to treat group

The Cox Proportional Hazards Model fitted with the core data given had a treatment variable coefficient of -0.3868 and a p-value of $p<0.001$. The coefficient shows that those who had the second treatment, BUP-NX, had a lower risk of failure than those who had XR-NTX. The hazard ratio was 0.6792, meaning that taking BUP-NX is associated with a reduction in risk by a factor of 0.6792. See Table 1 for more information. Another way this can be interpreted is that the BUP-NX treatment reduces the hazard by about 32%. Furthermore, the p-value of the variable is 0.000787 which is less than our significance threshold of 0.05 showing that this variable is indeed statistically important.

Table 1: Difference in relapse free survival in randomized controlled experiment

	Extended-Release Naltrexone (XR-NTX)	**Buprenorphine-Naloxone (BUP-NX)**
Number of Relapses (O_i)	164	140
Median Survival Time (Days) 95% CI	100 (66-135)	163 (126-NA)
Expected Number of Relapses (E_i)	137	167
Hazard Ratio 95% CI	0.68 (0.54-0.85)	
Log-Rank Test	$\chi^2 = 10.1$, 1 df, $p<0.001$	

Secondly, the treatment received was not the sole statistically significant estimator of survival time: the patient's rating of their weekly opiate cravings, the patient's quality of mental health over the past 30 days, whether the patient was white or not, and whether the patient had a history of skin conditions were all deemed to be confounding variables, which were in turn included as coefficients in our final Cox Proportional Hazards model. These findings bring to light factors that patients and their medical providers may seek to consider when assigning potential treatments for opioid relapse prevention.

After individually uncovering which variables might have an effect on time-to-relapse, we combined them into our final model. This Cox model initially consisted of which treatment a patient received (TRTNUM), whether they were White (DEWHITE) or Black (DEBLACK), their opiate use score (DSOPISCO), their average weekly opiate cravings (STRAT-OP-CR), whether they cared

about which treatment they received (CARED), whether they were satisfied with their living arrangements (AFLSSAT), their quality of mental health (QLMTLNG), and presence of a current skin condition, neurological damage, or schizophrenia (MHSKINC, MHNEURC, or MHSCHZC, respectively). For more information regarding the variables, see Tables 2 and 3.

When running our inital variables model through a Cox-stepwise-forward-selection model, we learned that TRTNUM, STRAT-OP-CR, QLMTLNG, DEWHITE, and MHSKINC should all be included in our final model. Thus our final model is as follows:

$$\begin{aligned}\lambda(t) = \lambda_0(t)\ \exp\ [&-0.406(\text{Treatment Type})_i + 0.406(\text{Weekly Opiate Craving Score})_i \\ &- 0.013(\text{Quality of Mental Health})_i - 0.301(\text{White Race})_i \\ &- 0.317(\text{Current Skin Condition})_i]\end{aligned} \tag{1}$$

The lambda coefficient is left uninterpreted and unspecified, with no assumptions to be made on its shape (7).

Holding all else constant, we can state that the hazard ratio (e^{coef}) for a patient's treatment was $e^{-0.406}$, meaning that those who received BUP-NX reduced their hazard by a factor of 0.666. Furthermore, the hazard ratio for the variable describing a patient's quality of mental health was $e^{-0.013}$, meaning that for each additional day a patient's mental health was "not good" in the past 30 days, their hazard decreased by a factor of 0.988. The hazard ratio for whether a patient was White was $e^{-0.301}$, meaning that for White patients, the hazard was reduced by a factor of 0.740. Additionally, the hazard ratio for patients with current skin conditions was $e^{-0.317}$, meaning that patients with skin disorders decrease the hazard by a factor of 0.729. Notably, the patient's opioid cravings were an important predictor of whether they relapsed or not. We found that for each additional 10 points of weekly opiate craving (on a scale of 0-100) the patient averaged over their duration in the study, their hazard was expected to multiply by a factor of 1.501 ($e^{0.406}$), holding all else constant.

Additionally, our comparison of the safety profile of the two treatments yielded the finding that there was no statistically significant difference between the two treatments, with regards to adverse events the patients experienced that were associated with the BUP-NX or XR-NTX medication.

Discussion

Our analysis had two major limitations: missing data and a lack of diversity among patients. Seventeen observations (patients) were removed from the final model due to missing values. Additionally, the patients in the study skewed white and male, with white patients accounting for 78.07% of all patients and males accounting for 70.35% of all patients. This lack of diversity limits the applicability of our final analysis.

Regarding assumptions, the Cox proportional hazards model assumes that covariates have a constant multiplicative effect on hazards over time (8). We believe this assumption is reasonable because a diagnostic plot of Schoenfeld residuals vs. survival times was randomly distributed about zero (7). A benefit of the Cox model is that no assumptions need to be made about the underlying hazard distribution to perform inference on covariate coefficients, and we have made no such assumptions here (7).

Future research might take into account the correlation between covariates to properly account for multicollinearity and produce more accurate results. Future work might also attempt to recruit a more diverse cohort of patients to obtain better insight into demographic covariates associated with time to relapse. Additionally, a more robust analysis of the safety profiles of both drugs might reveal underlying covariates related to adverse events.

References

[1] J. D. Lee, E. V. Nunes, P. Novo, K. Bachrach, G. L. Bailey, S. Bhatt, S. Farkas, M. Fishman, P. Gauthier, C. C. Hodgkins, J. King, R. Lindblad, D. Liu, A. G. Matthews, J. May, K. M. Peavy, S. Ross, D. Salazar, P. Schkolnik, D. Shmueli-Blumberg, D. Stablein, G. Subramaniam, J. Rotrosen, Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): A multicentre, open-label, randomised controlled trial, The Lancet 391 (10118) (2018) 309–318. doi:10.1016/S0140-6736(17)32812-X. 1, 2

[2] N. E. Hagemeier, Introduction to the opioid epidemic: the economic burden on the healthcare system and impact on quality of life, The American journal of managed care 24 (10 Suppl) (2018) S200—S206.
URL http://europepmc.org/abstract/MED/29851449 2

[3] N. Dasgupta, L. Beletsky, D. Ciccarone, Opioid Crisis: No Easy Fix to Its Social and Economic Determinants, American Journal of Public Health 108 (2) (2018) 182–186. doi:10.2105/AJPH.2017.304187. 2

[4] M. Reske, M. P. Paulus, Predicting treatment outcome in stimulant dependence, The New York Academy of Sciences 1141 (October 2008) 270–283. doi:10.1196/annals.1441.011.
URL https://nyaspubs.onlinelibrary.wiley.com/doi/full/10.1196/annals.1441.011 2

[5] T. M. Therneau, A Package for Survival Analysis in R, r package version 3.1-12 (2020).
URL https://CRAN.R-project.org/package=survival 2

[6] I.-H. S. C. Company, My.stepwise: Stepwise Variable Selection Procedures for Regression Analysis, r package version 0.1.0 (2017).
URL https://CRAN.R-project.org/package=My.stepwise 2

[7] Y. Jiang, Introduction to survival analysis (2) (2021). 4

[8] X. Xue, X. Xie, M. Gunter, T. E. Rohan, S. Wassertheil-Smoller, G. Y. Ho, D. Cirillo, H. Yu, H. D. Strickler, Testing the proportional hazards assumption in case-cohort analysis, BMC Medical Research Methodology 13 (1) (2013) 88. doi:10.1186/1471-2288-13-88. 4

Appendix

Table 2: Significant variables and their explanations (continued on Table 3)

Dataset	Variable	Explanation	Missing Values
ENROLL	TRTNUM	This variable is based on TRTSHOWN which is a categorical variable with values of either "XR-NTX" or "BUP-NX" per patient. We let this be a binary variable by setting "XR-NTX" to 0 and "BUP-NX" to 1.	Since there are no missing values within this variable, no wrangling for null values was necessary.
MOT	CARED	This variable is based on MOMEDANY which measures how much each patient cared about the treatment they received. We let this be a binary variable where values of 3, 4, and 5 were taken to mean that the patient did not care about the treatment and values of 1 and 2 were taken to mean that they did care which treatment they received.	Since there are no missing values within this variable, no wrangling for null values was necessary.
MHX	MHSKINC	This variable measures the presence of a skin condition at first office visit with 1 meaning the condition is present and 0 meaning not present.	The lack of an answer for any of these variables was treated as an absence of the condition (a 0). This leaves us with no null values.
	MHNEURC	This variable measures the presence of neurological damage at first office visit with 1 meaning the condition is present and 0 meaning not present.	
	MHSCHZC	This variable measures the presence of schizophrenia at first office visit with 1 meaning the condition is present and 0 meaning not present.	
VAS	STRAT-OP-CR	This variable is based on VACRVOPI which measures weekly opiate cravings on a scale of 0 to 100. After assigning numbers (0,10] the values of 1, (11,20] the values of 2, and so on, the average opiate craving for all weeks for each patient was calculated. As such, this variable contains values from 1 to 10 with 1 being the lowest opiate craving and 10 being the highest.	Since there were only two null values, the patients with those null values were dropped.
DSM	DSOPISCO	This variable measures the severity of opiate addiction on a scale of 1 to 5 with 1 being "Severe" and 5 being "None".	Since there are no missing values within this variable, no wrangling for null values was necessary.

Table 3: Continuation of Table 2

Dataset	Variable	Explanation	Missing Values
QLP	QLMTLING	This variable measures the quality of mental health. It answers the question "For how many of the past 30 days was your mental health not good?". Higher values indicate a higher incidence of bad mental health days and vice versa.	Since there are no missing values within this variable, no wrangling for null values was necessary.
DEM	DEWHITE	This variable is a binary variable detailing whether the patient identifies as White. 0 means the patient is not White and 1 means the patient is White.	No wrangling for null values was necessary.
	DEBLACK	This variable is a binary variable detailing whether the patient identifies as Black. 0 means the patient is not Black and 1 means the patient is Black.	
ASF	AFLSSAT	This variable measures whether the patient was satisfied with living conditions and has been mutated into a binary variable where the answer "YES" represented by 2 and 1 is 1 and the answer "NO" represented by 0 is 0.	Since there are no missing values within this variable, no wrangling for null values was necessary.