STA723 - Case Study 5

David Dunson

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Opioid pain relievers became widely prescribed in the late 1990s due to pharmaceutical company assurances that these drugs were not highly addictive. In 2017, the US declared a public health emergency around addiction to opioids, and in 2020, manufacturer Johnson & Johnson and three distributors agreed to a multi-billion dollar legal settlement, and legal issues around the opioid abuse and drug overdose crisis continue to be litigated. The CDC provides an overview of the epidemic at https://www.cdc.gov/drugoverdose/epidemic/index.html .

Detoxification and counseling-only care are standard treatments for opioid dependence in the US, despite high rates of relapse and overdose after detoxification. The US National Institute of Drug Abuse (NIDA) recently funded a clinical trial (CTN-0051) to explore comparative effectiveness of two pharmaceutical therapies for opioid dependence, which had been shown to be superior in prior studies when compared to counseling-only, but which had not been compared head-to-head. This study was designed to estimate the difference in opioid relapse-free survival between the two treatments, XR-NTX and BUP-NX. The study design and rationale, as well as the primary results, are available in two papers on Sakai.

Use of XR-NTX has been constrained by a number of factors, including high medication costs and a "detoxification hurdle." This drug is administered by injection approximately monthly. However, before treatment, patients must undergo complete detoxification and an opioid washout period, which is difficult for patients to accomplish.

BUP-NX is a partial opioid agonist and as such is controversial, as it is itself an opioid and is able to produce euphoria in people who are not dependent on opioids. The belief that this treatment just substitutes a new substance use disorder for an old one has hindered the adoption of this treatment. However, BUP-NX does not induce a high in individuals who have a high tolerance to opioids, but instead minimizes withdrawal symptoms and allows the

patient to function normally and participate in other recovery support services with the goal of managing the substance use disorder. It is an easier treatment to induce (start) because it does not require complete detoxification before treatment begins; however, patients need to take the medication daily on their own.

Questions of interest include the following. Refer to the data dictionary and two publications for questions regarding the data (the data have been slightly modified, but findings should be generally reproducible).

1. Is there a difference in time to relapse between patients randomized to BUP-NX and patients randomized to XR-NTX? This analysis is an intent to treat analysis and the standard for randomized controlled trials – even if patients are not successfully dosed with either treatment due to treatment induction failures, their outcomes are included in this comparison.

   (a) Are any patient-level or factors other than treatment assignment predictive of time to relapse? If so, what are they, and determine whether their associations with time to relapse differ across treatment groups.

   (b) While the primary study publication used a frequentist Cox proportional hazards model, you are encouraged to evaluate the adequacy of this model versus an accelerated failure time model.

2. Is there a difference in the proportion of patients successfully inducted into treatment with BUP-NX versus XR-NTX? Are there patient-level or other factors that are predictive of successful treatment induction, and if so, are their effects different across treatments? If there are factors that predict successful induction, are these factors also related to time to relapse? Comment on any concerns regarding potential sensitivity of analysis results to such factors.

3. A per protocol analysis differs from the intent to treat analysis by considering only those patients who were treated as intended. In this study, this means that the per protocol population includes only those patients who were randomized and who were successfully inducted onto an initial dose of the intended treatment. How do the results of the above analyses change if you conduct a per protocol analysis instead of intent to treat analysis?

4. Is there a difference in the safety profiles of the two treatments for any adverse events?