

Example of a SMART using Design I

1 Introduction

We consider the [ExTEND trial](#) (D. Oslin, P.I.) for managing alcoholism in individuals who do not respond to [naltrexone](#), an opioid receptor antagonist used for treatment of alcohol or opioid dependence.

2 Motivation

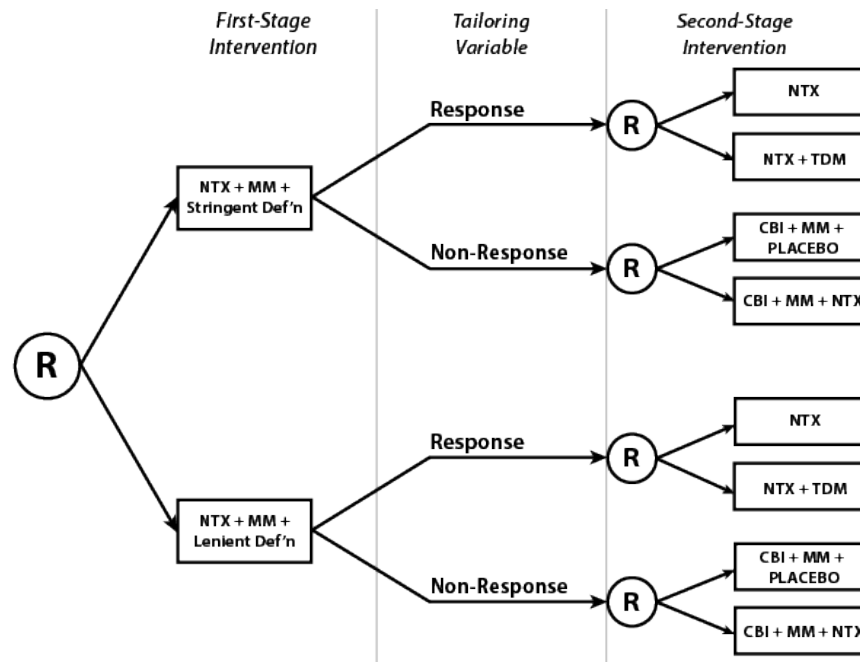
Naltrexone has been shown to be efficacious, but is infrequently prescribed by clinicians, due to observed low adherence and unanswered questions regarding follow-up treatments for individuals who do not respond. The main questions ExTEND sought to address were:

1. What level of drinking behavior constitutes non-response?
2. What second-stage treatment would be useful for individuals who do not respond to naltrexone?
3. What treatment would be useful for relapse prevention among individuals who respond to naltrexone?

3 Trial Components

The treatments under study are

1. Strict definition of non-response (2 or more days of heavy drinking in first 8 weeks)
2. Lenient definition of non-response (5 or more days of heavy drinking in first 8 weeks)
3. Naltrexone (NTX)
4. Telephone Disease Management (TDM)
5. Combined Behavioral Intervention (CBI)
6. Medical Management (MM)



In the first stage, individuals are randomized between a strict (2 or more heavy drinking days) and a lenient (5 or more heavy drinking days) definition of non-response. If this criterion is met, the individual is re-randomized to one of two rescue treatments; else, after 8 weeks, the participant is re-randomized to one of two “maintenance”, or relapse-prevention, treatments. Here, the tailoring variable is self-reported number of heavy drinking days.

4 Embedded Adaptive Interventions

There are eight adaptive interventions embedded in this design. They are

1. “Evaluate non-response under the strict definition. If the patient reports 2 or more days of heavy drinking in the first 8 weeks of treatment, switch to CBI, MM, and placebo. Otherwise, continue on NTX.”
2. “Evaluate non-response under the strict definition. If the patient reports 2 or more days of heavy drinking in the first 8 weeks of treatment, switch to CBI, MM, and placebo. Otherwise, augment NTX with TDM.”
3. “Evaluate non-response under the strict definition. If the patient reports 2 or more days of heavy drinking in the first 8 weeks of treatment, augment NTX with CBI and MM. Otherwise, continue on NTX.”
4. “Evaluate non-response under the strict definition. If the patient reports 2 or more days of heavy drinking in the first 8 weeks of treatment, augment NTX with CBI and MM. Otherwise, augment NTX with TDM.”

5. "Evaluate non-response under the lenient definition. If the patient reports 5 or more days of heavy drinking in the first 8 weeks of treatment, switch to CBI, MM, and placebo. Otherwise, continue on NTX."
6. "Evaluate non-response under the lenient definition. If the patient reports 5 or more days of heavy drinking in the first 8 weeks of treatment, switch to CBI, MM, and placebo. Otherwise, augment NTX with TDM."
7. "Evaluate non-response under the lenient definition. If the patient reports 5 or more days of heavy drinking in the first 8 weeks of treatment, augment NTX with CBI and MM. Otherwise, continue on NTX."
8. "Evaluate non-response under the lenient definition. If the patient reports 5 or more days of heavy drinking in the first 8 weeks of treatment, augment NTX with CBI and MM. Otherwise, augment NTX with TDM."

5 Outcome Measures

The primary outcome measures were percent of heavy drinking days and percent of drinking days over the last 8 weeks of the study.

References

- [1] Lei, H., Nahum-Shani, I., Lynch, K., Oslin, D., and Murphy, S. A. (2012), "A 'SMART' Design for Building Individualized Treatment Sequences," *Annu. Rev. Clin. Psychol.*, 8, 21-48.
- [2] Murphy, S. A., Lynch, K. G., Oslin, D. W., McKay, J. R., & Ten Have, T. R. (2007), "Developing adaptive treatment strategies in substance abuse research," *Drug Alcohol Dependence*, 88(2), S24-30. PMCID: PMC1922034