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Example of a SMART using Design A

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.

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:

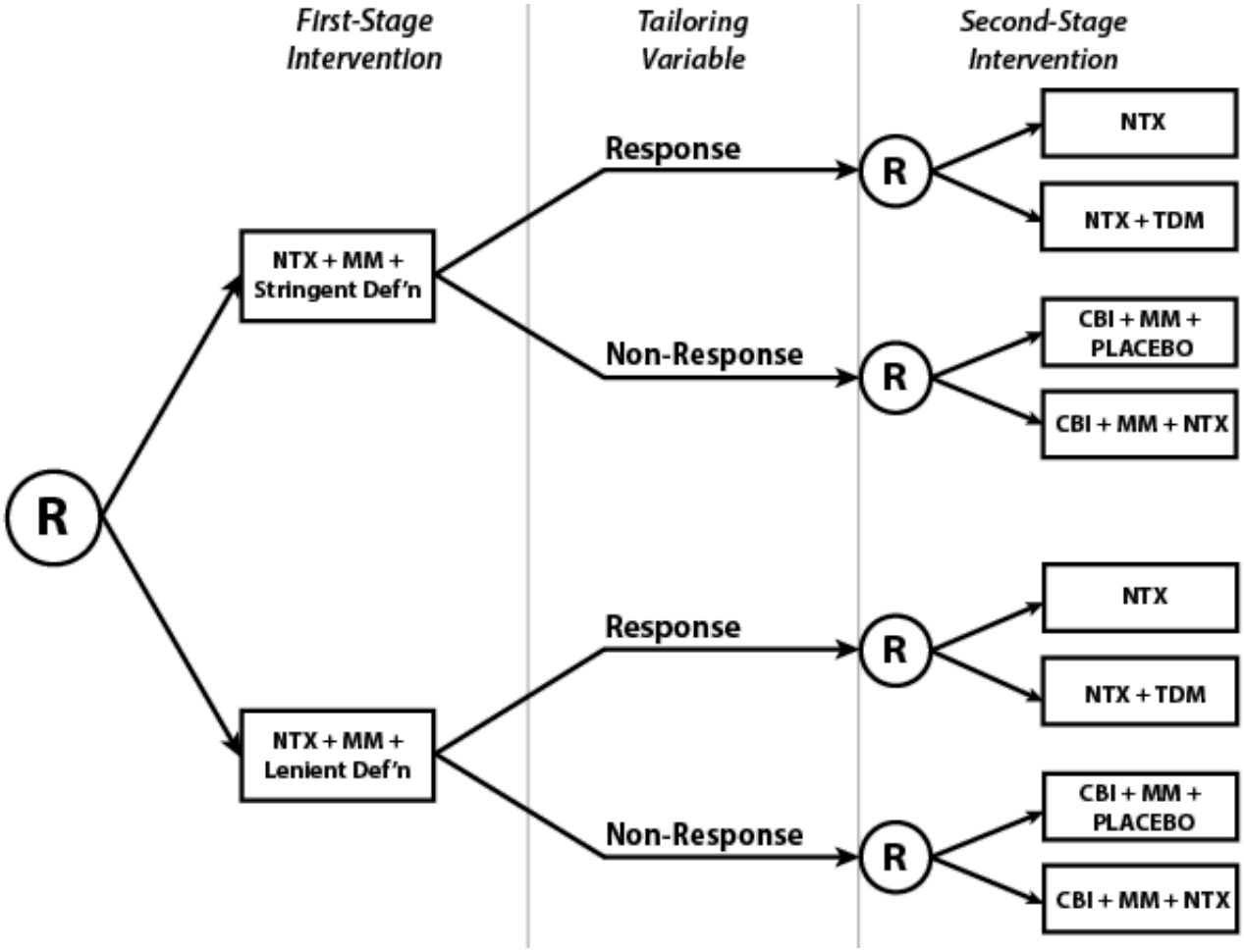
1. What level of drinking behavior constitutes non-response?
2. What second-stage treatment would be useful for individuals who do not respond to naltrexone?
3. What treatment would be useful for relapse prevention among individuals who respond to naltrexone?

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.



Embdedded Adaptive Interventions

There are eight adaptive interventions embedded in this design, as pictured above. 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."

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