A SMART Data Analysis Method for Constructing Adaptive Treatment Strategies in Substance Use Disorders

Inbal Nahum-Shani¹
Ashkan Ertefaie²
Xi Lu¹
Daniel Almirall¹
Kevin G. Lynch²
James R. McKay¹,³
David Oslin³
Susan A. Murphy¹

¹University of Michigan
²University of Pennsylvania
³Philadelphia Veterans Administration Medical Center

Technical Report Number 16-132

Copyright 2016, Penn State. All rights reserved.

Please send questions and comments to Inbal Nahum-Shani (corresponding author): Institute for Social Research, University of Michigan, Ann Arbor, Michigan 48106; inbal@isr.umich.edu


This work was supported by NIMH grants R01-MH-080015, R03-MH-097954; NIAAA grants: R01-AA-014851; P01-AA016821; RC1-AA-019092; NIDA grants R01-DA-039901, P50-DA-039838, P50-DA-010075; NICHD grant R01-HD-073975, U54-EB020404 (NIDCR, NIAMS, NHLBI, NIBIB, NIA). The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.
A SMART Data Analysis Method for Constructing Adaptive Treatment Strategies in Substance Use Disorders

Abstract

The cyclical and heterogeneous nature of many substance use disorders highlights the need to adapt treatment to accommodate the specific and changing needs of patients. Such modifications can be operationalized via adaptive treatment strategies—a treatment design in which treatment options are personalized over time based on baseline and time-varying patient information. The sequential, multiple assignment, randomized trial (SMART) was developed specifically for the purpose of constructing empirically-supported adaptive treatment strategies. Here, we provide an overview of Q-learning—a novel, straightforward method drawn from computer science. We use data from the ExTENd SMART study to demonstrate how weekly assessments of drinking behaviors can be used with Q-learning to empirically construct an adaptive treatment strategy employing naltrexone medication, behavioral intervention, and telephone disease management to reduce alcohol consumption over 24 weeks. This manuscript demonstrates the usefulness and accessibility of Q-learning to investigators in the area of substance use disorders.
Introduction

The cyclical and heterogeneous nature of many substance use disorders highlights the need to adapt the type or the dose of treatment to accommodate patients’ specific and changing needs. [1-4] Adaptive treatment strategies (ATSs) are suited for guiding this type of sequential and personalized treatment decision making. [1,5-8] An ATS is a treatment design in which treatment options are personalized (i.e., tailored) not only based on baseline characteristics (e.g., patient demographics), but also based on time-varying patient information, namely information that is likely to change over time in the course of treatment (e.g., early signs of non-response). Such adaptation is operationalized via decision rules that specify what type/dose of treatment should be offered, for whom and when. The sequential, multiple assignment, randomized trial (SMART) was developed specifically for constructing empirically supported ATSs. [9,10] A SMART is a randomized trial design, which involves multiple stages of randomization. Each randomization stage provides data that inform how best to personalize the treatment at a specific stage of an ATS (see details below).

Data analytic methods exist for comparing relatively simple ATSs embedded in a SMART. [11,12] However, investigators are often interested in using data from a SMART to construct ATSs that are more personalized than those embedded in the SMART. That is, investigators often collect additional information concerning baseline (e.g., baseline severity) and time-varying status of patients (e.g., adherence to treatment, side effects) and plan to use this information to investigate whether and how treatment could be further personalized according to these variables. Drawn from computer science, Q-learning [13,14] is a novel methodology that can be used for this purpose. The “Q” in Q-learning is used to indicate that this method is used to assess the relative quality of different treatment options in a sequence of personalized treatments.
Here, we use data from the ExTENd SMART study (D. Oslin, P.I. [15-17]) to demonstrate the usefulness and accessibility of Q-learning to investigators in the area of substance use disorders.

**Adaptive Treatment Strategies**

Consider the development of an ATS to treat alcohol dependence using oral naltrexone (NTX)—an opioid receptor antagonist that blocks the pleasurable effects resulting from endogenous opioid neurotransmitters released by alcohol consumption. [18,19] While NTX is efficacious for treating alcohol dependence, clinical use of NTX has been limited, [20] in part because of substantial heterogeneity in treatment response; [21] this heterogeneity is attributed to multiple barriers, such as poor adherence, biological response to the medication, poor coping skills, and poor social support. Hence, a natural ATS might include treatment components aimed to address these multiple barriers, such as combined behavioral intervention (CBI), an in-person intervention targeting adherence to pharmacotherapy, motivation for change and coping skills; and telephone disease management (TDM), targeting similar factors via basic (minimal) telephone-delivered clinical support. [22,23]

An example of an ATS for supporting NTX might be as follows: At the first-stage of this ATS, all patients are provided NTX, and their drinking behaviors are monitored weekly for eight weeks. At the second-stage of this ATS, the type of treatment is adapted based on the number of heavy drinking days (HDDs) in the past week, where a heavy drinking day is defined as four or more drinks per day for women and five or more for men. Specifically, patients who experience two or more HDDs during weeks three to eight are considered to be non-responding; as soon a patient is non-responding, s/he enters the second stage of this ATS and is offered a rescue intervention: adding CBI. Patients who never experience two or more HDDs up to and including week eight (the responding patients) are offered a maintenance intervention: adding TDM at the end of week eight. An ATS involves a sequence of decision rules; this ATS uses the decision rules in ATS#1 (Table 1).
Notice that the decision rules for this ATS involve a single tailoring variable—the patient’s response status. A tailoring variable is patient information used to make treatment decisions. Here, different second-stage treatments are offered to responders than to non-responders. The first-stage treatment and the criterion for non-response are not tailored; they are the same for all patients regardless of baseline information or patient characteristics.

Traditionally, the sequence of decision rules underlying ATSs used in practice are constructed based on clinical experience, empirical evidence and literature reviews. However, in many cases, there are open questions concerning the best treatment option at specific stages of an ATS, which tailoring variables to use, and how to best use them. For example, in the context of the example ATS above, there may be insufficient empirical or theoretical basis to inform (a) the amount of drinking behavior that reflects non-response to NTX, (b) the type of rescue tactic that would be most useful for non-responders, and (c) the type of maintenance tactic that would be most useful in reducing the chance of relapse among responders. The SMART is a clinical trial design that can be used to efficiently obtain data to address scientific questions such as these.

The Sequential, Multiple Assignment, Randomized Trial

A SMART is a multi-stage randomized trial. Participants progress through the stages and are potentially randomly assigned to one of several treatment options at each stage. Each stage of randomization is designed to address scientific questions concerning the type, dose, mode of delivery, or tailoring of treatments at a specific stage of an ATS. While most clinical trials are designed to evaluate or compare two or more treatments, SMART aims to provide data to construct and optimize an ATS.

As an example, consider the following simplified version of the ExTENd study. In this 24 week trial (Figure 1), NTX was offered to all participants. The first-stage randomization was to one of two
criteria for early non-response: (1) a stringent criterion, in which a participant was classified as a non-responder as soon as s/he had two or more HDDs during the first eight weeks of NTX treatment; or (2) a lenient criterion, in which a participant was classified as a non-responder as soon as s/he reported having five or more HDDs during the first eight weeks of NTX treatment. Participants were assessed weekly for drinking behavior. Starting at week three, as soon as the participant met his/her assigned criteria for non-response, s/he was immediately re-randomized to one of the two rescue tactics: (1) adding CBI (NTX+CBI) or (2) CBI alone (CBI). Participants who did not meet their assigned non-response criteria by the end of week eight (i.e., responders), were re-randomized at that point (i.e., at week 8) to one of two maintenance tactics: (1) adding TDM (NTX+TDM) or (2) NTX alone (NTX). The primary outcomes were based on weekly assessments of the number of drinking days.

Eight ATSs are embedded in the ExTENd design (see details in [15]); one is described above (ATS#1). Each embedded ATS utilizes one tailoring variable—the participant’s early response status. This is because, by design, different second-stage treatments were provided to responders than to non-responders. Various methods can be employed to compare and select the best ATSs among the eight that are embedded in ExTENd (see e.g., [11,25,26]). In previous analyses [15], ATS#1 was found to be the best among the eight ATSs in terms of the probability of drinking during the second-stage of treatment.

However, in this manuscript we seek to demonstrate how data arising from a SMART can be used to answer scientific questions beyond the comparison of embedded ATSs. In many cases investigators might wish to explore whether other variables, beyond response status, could be tailoring variables. For example, in ExTENd, it would be useful to explore whether the non-response criterion should be tailored to the patient’s baseline years of alcohol consumption. This is driven by empirical evidence suggesting that patients with more severe histories of alcohol use problems are prone to faster relapse, requiring a more stringent definition of non-response [27,28]. Additionally, it would be useful to
explore whether the maintenance tactic for responders should be based on the proportion of non-
abstinence (i.e., any use) days during the initial NTX treatment. This is based on the idea that although
any use of alcohol in the first few weeks of treatment is perhaps too low a threshold, early non-
abstinence places the patient at greater risk for poor long-term outcomes, hence requiring additional
support in order to maintain long-term improvement [29-31].

In the following section we demonstrate how Q-learning can be used to conduct these analyses
when the primary outcome is longitudinal.

**Q-Learning**

Q-learning [13,14] is a multi-stage regression approach which can be used with data from a
SMART to investigate whether and how certain covariates are useful for developing an ATS or
improving an existing one. Investigators first select a set of covariates at each stage which are
hypothesized to be useful tailoring variables for the randomized treatment options at that stage. Such
candidate tailoring variables may include any collection of baseline and time-varying variables
measured *in the past*, namely prior to the randomization at each stage. In Q-learning, a regression is used
at each stage to investigate whether and how treatment effect (i.e., the difference between treatment
options) at that stage varies as a function of the candidate tailoring variables, while appropriately
controlling for the effects of *future* tailored treatments. The Q-learning procedure is described in more
detail below in the context of our example. As will be seen, Q-learning resembles moderated regression
analyses [32], making it familiar and, therefore, easy to understand and implement. However, standard
moderated regression analyses typically cannot be used to examine time-varying covariates as candidate
tailoring variables for the purpose of developing an effective ATS. For example, Nahum-Shani et al.
[32] demonstrate how, compared to Q-learning, using a single moderated regression analysis to
investigate time-varying candidate tailoring variables in a sequential treatments setting can lead to bias and, therefore, misleading conclusions.

Here we describe the use of Q-learning using data from ExTENd study. As discussed above, two candidate tailoring variables would be useful to explore: (a) the patient’s baseline years of alcohol consumption (i.e., standardized number of years the patient consumed alcohol prior to entering the study; denoted $O_{11}$); and (b) the proportion of non-abstinence days during the first stage (denoted $O_{21}$). Notice that $O_{21}$ is an outcome of the first-stage NTX treatment, rather than a baseline measure.

Suppose that the primary outcome, $Y$, is the proportion of abstinence days over 24 weeks (high values are desirable). Let $A_1$ denote the randomized non-response criterion at the first randomization, coded -1 for the stringent criterion and 1 for lenient; $A_{2R}$ denote the randomized maintenance tactics for responders at the second randomization, coded -1 for NTX and 1 for NTX+TDM; $A_{2NR}$ denote the randomized rescue tactics for non-responders at the second randomization, coded -1 for CBI and 1 for NTX+CBI; and let $R$ denote the indicator for response ($R=1$) vs. non-response ($R=0$) to initial NTX.

To apply Q-learning in this context, we begin with the second stage randomization. A regression model for the primary outcome $Y$ among responders, conditional on ($O_{11}$, $A_1$, $O_{21}$, $A_{2R}$), is

$$\gamma_0 + \gamma_{21} O_{11} + \gamma_{22} A_1 + \gamma_{23} A_1 O_{11} + \gamma_{24} O_{21} + (\alpha_{21}^R + \alpha_{22}^R O_{21}) A_{2R}.$$ 

Our model for $Y$ in the regression for non-responders, conditional on ($O_{11}$, $A_1$, $O_{21}$, $A_{2NR}$), is

$$\gamma_0 + \gamma_{21} O_{11} + \gamma_{22} A_1 + \gamma_{23} A_1 O_{11} + \gamma_{24} O_{21} + \alpha_{21}^{NR} A_{2NR}.$$ 

We fit these regression models simultaneously to obtain the estimated regression coefficients. These regression coefficients can then be used to select the best rescue and maintenance tactics and assess the usefulness of $O_{21}$ in personalizing the best maintenance tactic. The best tactics are those for which the expected outcome attains its maximal value (i.e., the proportion of abstinence days over the study duration is maximal). Hence, we are mainly interested in the parameters $\alpha_{21}^R$ and $\alpha_{22}^R$ for
responders and $\alpha_{21}^{RN}$ for non-responders, because they contain information concerning the effect of the second-stage treatment options and (in the case of responders) whether and how this effect varies depending on the candidate tailoring variable $O_{21}$.

For responders, we use the formula $(\alpha_{21}^{R} + \alpha_{22}^{R}O_{21})$ to select the best maintenance tactic depending on $O_{21}$. If $(\alpha_{21}^{R} + \alpha_{22}^{R}O_{21}) > 0$, the maintenance tactic that maximizes the expected outcome is NTX+TDM ($A_{2R} = 1$); whereas if $(\alpha_{21}^{R} + \alpha_{22}^{R}O_{21}) < 0$ the maintenance tactic that maximizes the expected outcome is NTX alone ($A_{2R} = -1$). For non-responders, because no candidate tailoring variables are considered for the rescue tactics, we use the regression coefficient $\alpha_{21}^{RN}$ to select the best rescue tactic. If $\alpha_{21}^{RN} > 0$, the rescue tactic that maximizes the expected outcome is NTX+CBI ($A_{2NR} = 1$); whereas if $\alpha_{21}^{RN} < 0$, the rescue tactic that maximizes the expected outcome is CBI alone ($A_{2NR} = -1$).

After we have estimated the regression coefficients and assessed the evidence regarding the second-stage tactics and candidate tailoring variables, we move to the first randomization stage. In the case of ExTENd, the first randomization concerns the criterion for non-response. Here, we assess the evidence regarding this criterion and the candidate tailoring variable $O_{11}$, presuming that in the future we would employ the optimal maintenance tactic based on $O_{21}$ for responders and the optimal rescue tactic for non-responders. We do this by conducting another regression, where the dependent variable, $\tilde{Y}$, is the estimated outcome under the optimal second-stage treatment option: this is $\tilde{Y} = \hat{\gamma}_{20} + \hat{\gamma}_{21}O_{11} + (\hat{\alpha}_{21}^{R} + \hat{\alpha}_{22}^{R}O_{21})$ for responders, and $\tilde{Y} = \hat{\gamma}_{20} + \hat{\gamma}_{21}O_{11} + \hat{\gamma}_{22}A_{1} + (\hat{\alpha}_{21}^{RN})$ for non-responders.

Next, we regress $\tilde{Y}$ on the predictors using the model:

$$\gamma_{10} + \gamma_{11}O_{11} + (\alpha_{11} + \alpha_{12}O_{11})A_{1}.$$ 

This model can then be used to select the best non-response criterion and assess the usefulness of $O_{11}$ in personalizing the best non-response criterion. Specifically, we use the formula $(\alpha_{11} + \alpha_{12}O_{11})$ to select
the best non-response criterion, depending on the candidate tailoring variable $O_{11}$. If $(\alpha_{11} + \alpha_{12}O_{11}) > 0$, the lenient criterion ($A_1 = 1$) leads to the highest expected outcome under the optimal second-stage treatment option; whereas if $(\alpha_{11} + \alpha_{12}O_{11}) < 0$, the stringent criterion ($A_1 = -1$) leads to the highest expected outcome under the optimal second-stage treatment option.

**Illustrative Analysis of the ExTENd Data**

The procedure described above was implemented to analyze data from the ExTENd study, using the ‘qlearning’ package in R [33]. Information from a total of 250 study participants was used in this analysis. Multiple imputation methodology, adapted for the SMART setting [34], was implemented to adjust for the missing data (see Lu et al. [35]). Appendix 1 includes information concerning missing data, as well as the baseline characteristics of study participants.

**Measures**

Weekly time-line follow-back (TLFB) assessments of the number of standard drinks recorded per day were used to calculate (a) the primary outcome ($Y$)–the proportion of abstinence days over the study duration–by dividing the number of non-drinking days by the duration of the study (i.e., higher values are preferable); and (b) the proportion of non-abstinence days during the initial NTX treatment ($O_{21}$), by dividing the number of drinking days by the total number of days the participant was provided the initial NTX treatment (i.e., the total number of days in the first stage prior to re-randomization). Baseline years of alcohol consumption ($O_{11}$) was self-reported by patients prior to initial randomization. Participants were asked to indicate the number of years they consumed alcohol (i.e., any use) prior to entering the study (see Appendix 1 for sample distributions of variables).
Data Analysis

We used the Q-learning procedure described above to analyze the data. In both the first- and second-stage regressions we included an indicator of gender (female=1) as a covariate. The estimated regression coefficients and associated lower and upper limit of the 90\% confidence intervals (CI) are summarized across 10 imputed datasets using the approach recommended by Shortreed and colleagues [34].

Results

Table 2 includes the results for the second-stage regression, which aims to select the best rescue and maintenance tactics and to assess the usefulness of the proportion of non-abstinence days during the initial NTX treatment ($O_{21}$) in personalizing the best maintenance tactic. The coefficient of $A_{2NR}$ is not significantly different from zero ($\hat{\alpha}^{NR}_{21} = -.02; CI = [-.06, .04]$), indicating inconclusive evidence with respect to the difference between the two rescue tactics for non-responders.

For responders, the interaction between $A_{2R}$ and $O_{21}$ was significantly different from zero ($\hat{\alpha}^{R}_{22} = .14; CI = [.06, .24]$), indicating that the effect of maintenance tactics for responders varies depending on the proportion of non-abstinence days during initial NTX treatment. To understand how this effect varies, we estimated the formula ($\hat{\alpha}^{R}_{21} + \hat{\alpha}^{R}_{22}O_{21}$) for various levels of $O_{21}$ (see Table 2). Results indicate that for responders who consumed alcohol during 10\% or less of the days during the initial NTX treatment, the term ($\hat{\alpha}^{R}_{21} + \hat{\alpha}^{R}_{22}O_{21}$) was not significantly different from zero (e.g., for $O_{21} = .1, \hat{\alpha}^{R}_{21} + 0.1\hat{\alpha}^{R}_{22} = .02; CI = [-.001, .03]$). However, for responders who consumed alcohol during more than 10\% of the days during the initial NTX treatment, the term ($\hat{\alpha}^{R}_{21} + \hat{\alpha}^{R}_{22}O_{21}$) was positive and significantly different from zero (e.g., for $O_{21} = .2, \hat{\alpha}^{R}_{21} + .2\hat{\alpha}^{R}_{22} = 0.03; CI = [.01, .06]$). For these responders (33\% of all study responders), adding TDM (i.e., $A_{2R} = 1$) leads to at least a 6\%ii (i.e., 10
days on average) increase in the proportion of abstinence days over the entire study duration, relative to continuing NTX alone (i.e., $A_{2R} = -1$).

After assessing the evidence regarding the second-stage tactics and candidate tailoring variables, we move to the first randomization stage. Here, the goal is to select the best non-response criterion and to assess the usefulness of baseline years of alcohol consumption ($O_{11}$) in personalizing the non-response criterion. Recall that this is evaluated under the assumption that in the future we would employ the optimal maintenance tactic based on $O_{21}$ for responders and the optimal rescue tactic for non-responders.

The results for the first-stage regression are included in Table 3. Based on the estimated regression coefficients we estimated the formula $(\alpha_{11} + \alpha_{12}O_{11})$ for high (1 SD above the sample mean) and low (1 SD below the sample mean) values of $O_{11}$. Neither regression coefficient was significantly different from zero. This indicates that there is inconclusive evidence with respect to the difference between the two non-response criteria, regardless of the baseline years of alcohol consumption. Indeed, the term $(\alpha_{11} + \alpha_{12}O_{11})$ was not significantly different from zero for high $(\hat{\alpha}_{11} + \hat{\alpha}_{12} = .002, CI = [-.03, .03])$, or low $(\hat{\alpha}_{11} - \hat{\alpha}_{12} = .02, CI = [-.01, .05])$ values of $O_{11}$. The ATS proposed based on these analyses is presented in Table 1 (ATS #2).

**Discussion**

Consistent with previous studies [15], in additional analyses we found ATS#1 to be the best of the 8 ATSs embedded in the ExTENd study in terms of the proportion of abstinence days over the study duration; that is, it was the best among the eight ATSs in which response status was used as the sole tailoring variable. The proportion of abstinence days over the entire study duration among participants following ATS#1 (Table 1) was estimated to be 78%. Our Q-learning analyses indicates that ATS#2-- in which the proportion of non-abstinence days during the initial NTX treatment was used as a tailoring
variable in addition to response status—produces the same outcomes (i.e., 78% abstinence days over the entire study duration) while reducing treatment costs and burden in the process.

Specifically, the strategy informed by Q-learning (ATS #2) is advantageous in that it recommends NTX+TDM only to a subset of responders, namely those for whom the proportion of non-abstinence days during the initial NTX treatment was larger than 10%. Hence, while ATS #1 recommends that TDM should be added to all responders, the more personalized ATS (ATS #2) recommends TDM to only 33% of responders. Although TDM is a cost-effective and potentially cost-saving strategy for treating substance use disorders compared to face-to-face alternatives [39], costs per session are estimated at $30.24 for the client and $30.55 for the health system [40]. Hence, employing ATS#2 will likely result in substantially lower societal cost, while achieving the same outcomes as ATS#1.

This has potential implications on both the scalability of the ATS as well as on participant adherence. First, offering more costly treatments only to those who need it most should lead to greater cost-effectiveness, enhancing the scalability of substance abuse treatments (6). Second, providing no more intervention than needed will reduce treatment burden, hence improve treatment adherence [41]. This demonstrates how ATSs generated by Q-learning have the potential to improve the treatment of substance abuse beyond ATSs that are embedded in a SMART study, informing the development of personalized treatment protocols that optimize outcomes while reducing cost and treatment burden [42].

**Conclusion**

This manuscript illustrates how longitudinal data arising from a SMART can be used with Q-learning to identify new ways to personalize treatments based on dynamic, ongoing information collected during treatment. Specifically, our illustrative analysis suggests that even responders to NTX treatment can be heterogeneous, with some exhibiting more drinking behaviors than others during
treatment. This information was useful in identifying those patients who respond well to NTX but require more support to maintain progress. Hence, our application of Q-learning demonstrates how this novel methodology can contribute to the development of more cost-effective, stepped-care strategies for treating substance use disorders like alcohol dependence.
References


Figure 1. ExTENd SMART study
<table>
<thead>
<tr>
<th>Table 1. Adaptive treatment strategies</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>ATS #1</th>
<th>ATS #2: A more deeply tailored ATS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At entry into the program</strong></td>
<td><strong>At entry into the program</strong></td>
</tr>
<tr>
<td>First-stage treatment = [NTX]</td>
<td>Stage 1 treatment = [NTX]</td>
</tr>
<tr>
<td><strong>At the end of every week from week 3 to 8 of the initial NTX treatment</strong></td>
<td><strong>By the end of week 3 of initial NTX treatment</strong></td>
</tr>
<tr>
<td>If response status = nonresponse (HDD ≥ 5) Then, second-stage treatment = [Switch to CBI immediately]</td>
<td>Choose between a stringent or lenient criterion for weekly response/non-responseiii</td>
</tr>
<tr>
<td>Else if response status = response (HDD &lt; 5) Then, continue first-stage treatment and re-assess non-response in the following week, and at week 8 move to second-stage treatment = [add TDM]</td>
<td><strong>At the end of every week from week 3 to 8 of the initial NTX treatment</strong></td>
</tr>
<tr>
<td>If response status = non-response Then, second-stage treatment = [offer CBI or NTX+CBI]</td>
<td><strong>Else if response status = response</strong></td>
</tr>
<tr>
<td>Else if response status = response Then, continue stage 1 treatment and re-assess non-response in the following week, and, at week 8 If the proportion of non-abstinence days during first-stage &gt; 10% Then, move to second-stage treatment = [NTX+TDM]</td>
<td><strong>Else if the proportion of non-abstinence days during first-stage ≤ 10%</strong></td>
</tr>
<tr>
<td>Else, move to second-stage treatment = [NTX+TDM or NTX alone]</td>
<td><strong>Then</strong>, move to second-stage treatment = [NTX+TDM]</td>
</tr>
</tbody>
</table>
Table 2. Results for second-stage model for responders and estimated \((\alpha_{21}^R + \alpha_{22}^R O_{21})\)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.06</td>
<td>-0.15, -0.03</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.03</td>
<td>-0.08, 0.02</td>
</tr>
<tr>
<td>(O_{11}): Baseline years of alcohol consumption</td>
<td>-0.003</td>
<td>-0.02, 0.02</td>
</tr>
<tr>
<td>(A_1): Nonresponse criterion</td>
<td>0.01</td>
<td>-0.01, 0.03</td>
</tr>
<tr>
<td>(O_{21}): Percent drinking days during stage 1</td>
<td>-1.07</td>
<td>-1.20, -0.96</td>
</tr>
<tr>
<td>(A_{2R}): Maintenance tactic for responders</td>
<td>0.003</td>
<td>-0.02, 0.02</td>
</tr>
<tr>
<td>(A_{2NR}): Rescue tactic for non-responders</td>
<td>-0.02</td>
<td>-0.06, 0.04</td>
</tr>
<tr>
<td>(A_{2R} \times O_{21}): Maintenance tactic for responders x Percent drinking days during stage 1</td>
<td>0.14</td>
<td>0.06, 0.24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estimated ((\alpha_{21}^R + \alpha_{22}^R O_{21}))</th>
<th>Estimate</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent drinking days during stage 1 ((O_{21})= 0) ((24% \text{ of responders had } O_{21}=0))</td>
<td>0.003</td>
<td>-0.02, 0.02</td>
</tr>
<tr>
<td>Percent drinking days during stage 1 ((O_{21})= 0.1) ((43% \text{ of responders had } 0&lt; O_{21} \leq 0.1))</td>
<td>0.02</td>
<td>-0.001, 0.03</td>
</tr>
<tr>
<td>Percent drinking days during stage 1 ((O_{21})= 0.2) ((14% \text{ of responses had } 0.1&lt; O_{21} \leq 0.2))</td>
<td>0.03</td>
<td>0.01, 0.06</td>
</tr>
<tr>
<td>Percent drinking days during stage 1 ((O_{21})= 0.3) ((10% \text{ of responders had } 0.2&lt; O_{21} \leq 0.3; \text{ and } 9% \text{ had } 0.3&lt; O_{21}))</td>
<td>0.05</td>
<td>0.02, 0.08</td>
</tr>
</tbody>
</table>
Table 3. Results for first-stage model and estimated \((\alpha_{11} + \alpha_{12}O_{11})\)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.21</td>
<td>-0.37</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.06</td>
<td>-0.15</td>
</tr>
<tr>
<td>(O_{11}): Baseline years of alcohol consumption</td>
<td>-0.0001</td>
<td>-0.02</td>
</tr>
<tr>
<td>A(_1): Nonresponse criterion</td>
<td>0.01</td>
<td>-0.02</td>
</tr>
<tr>
<td>A(<em>1) (\times) (O</em>{11}): Non-response criterion (\times) Baseline years of alcohol consumption</td>
<td>-0.01</td>
<td>-0.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estimated ((\alpha_{11} + \alpha_{12}O_{11}))</th>
<th>Estimate</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients with low number of baseline years of alcohol consumption (i.e., (O_{11} = -1), namely 1 SD below sample mean)</td>
<td>0.02</td>
<td>-0.01</td>
</tr>
<tr>
<td>For patients with high number of baseline years of alcohol consumption (i.e., (O_{11} = 1), namely 1 SD above sample mean)</td>
<td>0.002</td>
<td>-0.03</td>
</tr>
</tbody>
</table>
FOOTNOTES

i We set the type I error rate to 0.10, rather than 0.05, given the illustrative nature of this analysis. Moreover, the aim of the analysis is to generate hypotheses about useful tailoring variables. Hence, from a clinical standpoint, it is sensible to tolerate a greater probability of detecting a false effect in order to improve the ability to detect true effects (see Collins et al. [36]; Dziak et al. [37]; McKay et al.,[38]).

ii Since we used effect coding, the estimated average difference between TDM (i.e., $A_{2R} = 1$) and NTX alone (i.e., $A_{2R} = -1$) is twice the term ($\hat{\alpha}_{21}^R + 2\hat{\alpha}_{22}^R$), that is 0.06.

iii The selection might be based on patient preference, clinical expertise, feasibility concerns, or other individual factors.