European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

www.elsevier.com/locate/euroneuro

An analysis of moderators in the COMBINE study: Identifying subgroups of patients who benefit from acamprosate ☆

Ralitza Gueorguieva[a,*], Ran Wu[b], Wan-Min Tsai[a], Patrick G. O'Connor[c], Lisa Fucito[b], Heping Zhang[a], Stephanie S. O'Malley[b]

[a]*Department of Biostatistics, Yale University School of Public Health and School of Medicine, New Haven, CT 06520, USA*
[b]*Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06519, USA*
[c]*Department of Internal Medicine, Yale University School of Medicine, New Haven, CT 06519, USA*

Received 18 March 2015; received in revised form 28 May 2015; accepted 12 June 2015

KEYWORDS
Alcohol dependence;
Moderator effects;
Classification and regression trees;
Subgroups with enhanced treatment effect;
Clinical trials

Abstract
The goal of the current study was to use tree-based methods to identify moderators of acamprosate effect on abstinence from heavy drinking in COMBINE, the largest study of pharmacotherapy for alcoholism in the United States to date. We used three different tree-based methods for identification of subgroups with enhanced treatment response on acamprosate based on over 100 predictors measured at baseline in COMBINE. No heavy drinking during the last two months of treatment was the considered outcome. All three methods identified consecutive days of abstinence prior to treatment as the most important moderator of treatment effect. Acamprosate was beneficial for participants with shorter abstinence (1 week or less) especially when body mass index was low or normal. In this group, 46% of participants receiving active acamprosate abstained from heavy drinking compared to 23% of those receiving placebo acamprosate. Prior treatment, age, drinking goal and cognitive inefficiency were identified as moderators of acamprosate effects by one of the three methods. In conclusion, acamprosate may be beneficial for participants with shorter abstinence who are not overweight or obese. One hypothesis for this finding is that this subgroup may have greater glutamatergic hyperactivity, a target of acamprosate, and may achieve better drug plasma levels based on their lower BMI. In contrast, those with extended pretreatment abstinence who have an

☆The project described was supported by Grants R01AA017173, K05 AA014715, P50 AA012870 and K23 AA020000 from the National Institute on Alcohol Abuse and Alcoholism. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Alcohol Abuse and Alcoholism or the National Institutes of Health. The sponsor had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

*Corresponding author at: 60 College St., New Haven, CT 06520-8034, USA. Tel.: +1 203 285 8155; fax: +1 203 785 6912.
E-mail address: ralitza.gueorguieva@yale.edu (R. Gueorguieva).

http://dx.doi.org/10.1016/j.euroneuro.2015.06.006

Please cite this article as: Gueorguieva, R., et al., An analysis of moderators in the COMBINE study: Identifying subgroups of patients who benefit from acamprosate. European Neuropsychopharmacology (2015), http://dx.doi.org/10.1016/j.euroneuro.2015.06.006

otherwise good prognosis did not benefit from acamprosate. Further validation of the results in independent data sets is necessary.

1. Introduction

The primary objective of randomized clinical trials is to assess average treatment effects: that is, how much the treatment effects differ on average across participants within each condition. However, due to between-subject heterogeneity, treatments may work well in one subset of the population and may be less effective in another subset. For such treatments, it is hard to show an average beneficial effect and hence these treatments may be underutilized in a population for which they might provide significant benefit. This is a particularly troublesome issue in clinical trials of treatments for alcohol dependence characterized by high patient heterogeneity and where treatment effects are typically in the small to medium range. To address this issue it has become necessary to explore moderator effects, i.e. to identify specific baseline covariates that stratify the population into subgroups for which treatment has differential effects (Kraemer et al., 2002). However, the usual approach has been to consider baseline predictors one at a time (e.g., Ray and Hutchison, 2007) or to test treatment effects among predefined endophenotypes (e.g., Mann et al., 2009). In COMBINE, the largest clinical trial of treatments for alcoholism to date in the United States (Anton et al., 2006) only individual predictors/moderators of treatment effects (naltrexone, acamprosate, CBI) have been considered (e.g. Anton et al., 2008) or "unsupervised" clustering methods have been applied (Bogenschutz et al., 2008). Since covariates are often related to each other and subpopulations are defined by combinations of predictor variables, it is of limited use to consider only main effects of predictors. Furthermore, an easy interpretation is essential for translating findings from clinical trials into clinical practice.

Tree-based and forest-based methods address the limitations of considering predictors one at a time and are considered "supervised learning" approaches. Classical decision trees (Breiman et al., 1984; Zhang and Singer, 2010) identify combinations of patient characteristics associated with good outcome overall, i.e. they identify which variables interact with one another to produce a certain classification. This is done via recursive partitioning by dividing the study sample recursively into groups that are most homogeneous with respect to the outcome and most distinct from one another. Different versions of the algorithm incorporate different statistical criteria for splitting the sample and determining the optimal size of the tree.

Tree-based methods are appealing alternatives to standard linear model techniques when assumptions of additivity of the effects of explanatory variables, normality and linearity are untenable. Tree-based and forest-based methods are nonparametric computationally intensive algorithms that can be applied to large data sets and are resistant to outliers. They allow consideration of a large pool of predictor variables and can discover predictors that even experienced investigators may have overlooked (Zhang et al., 2010). These methods are most useful for identification of variable interactions and may be easier to use in clinical settings because they require evaluation of simple decision rules rather than mathematical equations (Zhang and Singer, 2010).

Prior analysis of the COMBINE data using classical tree-based approaches (Gueorguieva et al., 2014) identified longer abstinence, drinking goal of total abstinence and older age as predictive of lower probability of heavy drinking during the last two months of double-blind treatment irrespective of treatment. However, the tree-based methods did not identify interactions involving treatment and thus did not consider moderating effects of the various treatments. Several distinct methods which represent modifications of decision trees have been proposed in recent years (Zhang et al., 2010; Foster et al., 2011, Lipkovich and Dmitrienko, 2014). Each of these methods allows identification of subgroups of participants for whom there are significant differences in effectiveness of treatments and thus could be useful in identifying moderators. In the current study we apply each of these three different methods to identification of moderators of acamprosate effects and evaluate the consistency of the conclusions from these three approaches.

The COMBINE Study evaluated the benefits of combining pharmacotherapy treatment (naltrexone, acamprosate) and behavioral interventions (Medication Management (MM) (Pettinati et al., 2004), Combined Behavioral Intervention (CBI), (Miller, 2004)) in alcohol dependent patients. In the primary analyses of the study, naltrexone (+MM) and CBI (+MM) were associated with improved outcome. However, participants on acamprosate did not have significantly better outcome than participants on placebo (Anton et al., 2006). Despite the absence of an average treatment effect of acamprosate, it is possible that there are subgroups of patients for whom acamprosate is beneficial. In particular, acamprosate is hypothesized to affect negative reinforcement of addictive behavior (Littleton, 1995; Mann et al., 2008) and hence pretreatment commitment to abstinence (Hall et al., 1990a) could be an important moderator of treatment response. Consistent with this, acamprosate has been found to be effective among those who were committed to abstinence (Mason et al., 2006). There is also evidence that acamprosate may be helpful for alleviating withdrawal symptoms during initial alcohol abstinence such as sleep disturbance (Perney et al., 2012; Staner et al., 2006). In previous analyses by our group, acamprosate appeared to "rescue" early non-compliers to CBI (Gueorguieva et al., 2014) and baseline trajectories of drinking moderated acamprosate response (Gueorguieva et al., 2011) such that acamprosate was counter-therapeutic for daily drinkers who achieved a longer period of abstinence prior to treatment.

Please cite this article as: Gueorguieva, R., et al., An analysis of moderators in the COMBINE study: Identifying subgroups of patients who benefit from acamprosate. European Neuropsychopharmacology (2015), http://dx.doi.org/10.1016/j.euroneuro.2015.06.006