Drug and Alcohol Dependence 130 (2013) 45–51

Contents lists available at SciVerse ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Fine-grain analysis of the treatment effect of topiramate on methamphetamine addiction with latent variable analysis

Jennie Z. Ma[a,*], Bankole A. Johnson[b], Elmer Yu[c], David Weiss[d], Frances McSherry[d], Jim Saadvandi[e], Erin Iturriaga[f], Nassima Ait-Daoud[b], Richard A. Rawson[g], Mark Hrymoc[g], Jan Campbell[h], Charles Gorodetzky[h], William Haning[i], Barry Carlton[i], Joseph Mawhinney[j], Dennis Weis[k], Michael McCann[l], Tony Pham[l], Christopher Stock[m], Ruth Dickinson[m], Ahmed Elkashef[f], Ming D. Li[b]

[a] Department of Public Health Sciences, University of Virginia, P.O. Box 800717, Charlottesville, VA 22908, USA
[b] Department of Psychiatry and Neurobehavioral Sciences, University of Virginia, Charlottesville, VA 22908, USA
[c] Veterans Administration Medical Center, Philadelphia, PA 19104, USA
[d] Department of Veterans Affairs Cooperative Studies Program Coordinating Center, Perry Point, MD 21902, USA
[e] Information Management Consultants, Reston, VA 22191, USA
[f] National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD 20892, USA
[g] UCLA Integrated Substance Abuse Programs, Los Angeles, CA 90025, USA
[h] Department of Psychiatry, University of Missouri, Kansas City, MO 64131, USA
[i] Pacific Addiction Research Center, Honolulu, HI 96813, USA
[j] South Bay Treatment Center, San Diego, CA 92105, USA
[k] Lutheran Hospital Office of Research, Des Moines, IA 50309, USA
[l] Matrix Institute on Addictions, West Los Angeles, CA 90025, USA
[m] Department of Veterans Affairs, Salt Lake City Health Care System, Salt Lake City, UT 84148, USA

ARTICLE INFO

Article history:
Received 11 January 2012
Received in revised form 12 October 2012
Accepted 14 October 2012
Available online 9 November 2012

Keywords:
Addiction
Methamphetamine
Topiramate
Latent variable analysis

ABSTRACT

Background: As reported previously, 140 methamphetamine-dependent participants at eight medical centers in the U.S. were assigned randomly to receive topiramate ($N = 69$) or placebo ($N = 71$) in a 13-week clinical trial. The study found that topiramate did not appear to reduce methamphetamine use significantly for the primary outcome (i.e., weekly abstinence from methamphetamine in weeks 6–12). Given that the treatment responses varied considerably among subjects, the objective of this study was to identify the heterogeneous treatment effect of topiramate and determine whether topiramate could reduce methamphetamine use effectively in a subgroup of subjects.
Methods: Latent variable analysis was used for the primary and secondary outcomes during weeks 6–12 and 1–12, adjusting for age, sex, and ethnicity.
Results: Our analysis of the primary outcome identified 30 subjects as responders, who either reduced methamphetamine use consistently over time or achieved abstinence. Moreover, topiramate recipients had a significantly steeper slope in methamphetamine reduction and accelerated to abstinence faster than placebo recipients. For the secondary outcomes in weeks 6–12, we identified 40 subjects as responders (who had significant reductions in methamphetamine use) and 65 as non-responders; topiramate recipients were more than twice as likely as placebo recipients to be responders (odds ratio = 2.67; $p = 0.019$). Separate analyses of the outcomes during weeks 1–12 yielded similar results.
Conclusions: Methamphetamine users appear to respond to topiramate treatment differentially. Our findings show an effect of topiramate on the increasing trend of abstinence from methamphetamine, suggesting that a tailored intervention strategy is needed for treating methamphetamine addiction.

1. Introduction

Methamphetamine is used and misused as a central nervous system stimulant and acts primarily by increasing the release of stored catecholamine such as dopamine, epinephrine, and norepinephrine (Kuczenski, 1983). It also inhibits monoamine oxidase, an action that would increase its catecholaminergic activity (Kuczenski, 1983). Methamphetamine readily enters the central nervous system, where it has a marked stimulant effect on mood and alertness (Fleckenstein et al., 2007; Cruickshank and Dyer, 2009). Because of its easy production in clandestine laboratories with relatively inexpensive over-the-counter ingredients, and because it is a powerful

* Corresponding author. Tel.: +1 434 243 5778; fax: +1 434 243 5787.
E-mail address: jzm4h@virginia.edu (J.Z. Ma).

0376-8716/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.drugalcdep.2012.10.009

psychostimulant, methamphetamine has become a major drug of abuse in the United States and other countries (Suwaki, 1991; Klee, 1992; U.S. Department of Health and Human Services, 2007). Methamphetamine users exhibit signs and symptoms such as violent behavior, anxiety, confusion, insomnia, and psychotic features such as paranoia and mood disturbances. Clinically, methamphetamine toxicity manifests in nearly every organ system, with the most dramatic changes being observed in the cardiovascular system and brain, causing cardiovascular disease, brain damage, and death (Fleckenstein et al., 2007; Cruickshank and Dyer, 2009).

Despite a decade of intensive research, effective pharmacotherapy for stimulant dependence remains elusive, with a noted lack of controlled clinical trials studying methamphetamine abuse in particular (Ling and Shoptaw, 1997; Cruickshank and Dyer, 2009). Topiramate is an anticonvulsant drug that can treat craving for alcohol, nicotine, and cocaine as well as eating disorders (Zullino et al., 2002; Johnson et al., 2003, 2005; Kampman et al., 2004; Leombruni et al., 2009). To investigate the efficacy of topiramate in treating methamphetamine addiction, a 13-week multi-site, placebo-controlled randomized trial was conducted (Elkashef et al., 2012). The study had mixed findings in that topiramate did not appear to promote weekly abstinence significantly in methamphetamine users (primary outcome), but it did reduce the weekly median urine methamphetamine concentration (secondary outcome; Elkashef et al., 2012).

Many studies in addiction and drug abuse have focused on the evaluation of the effectiveness of a treatment based on the relations between outcomes and various clinical factors (Hartz et al., 2001; Johnson et al., 2003; Ma et al., 2006; Shoptaw et al., 2006). However, because a participant might respond better on some outcomes than others, it is possible to achieve mixed or even conflicting efficacy results; i.e., the treatment appears to be effective by one outcome measure but ineffective by others. Another challenge is the heterogeneity of the subjects. In the case of methamphetamine research, there is pathological or clinical evidence of a differential disease process with differently expressed symptoms (Srisurapanont et al., 2001; Kaye et al., 2007; Wu et al., 2009). Consequently, not all subjects who are methamphetamine dependent would be expected to respond equally to a given treatment. Thus, an analytical approach that can account for the potential heterogeneity in outcomes would be crucial in identifying subjects for whom certain treatments are effective.

Latent variable analysis has recently stimulated interest in identifying potential heterogeneity by profiling patients with respect to multiple risk factors or multivariate outcome measures (Gueorguieva et al., 2011). The key concept of such analytical approaches is to use latent variables (not directly observable but inferred from data) to explain the observed variables and to identify unobserved population stratification or clustering. Specifically, latent class analysis (LCA) is used to identify the unobserved groups or predictors of those classes for multivariate categorical data (McCutcheon, 1987; Keel et al., 2004), whereas the latent growth mixture model (LGMM) is used to identify unobserved population heterogeneity by modeling the longitudinal trajectories or growth curves for longitudinal data (Muthén et al., 2002; Connell and Frye, 2006; Stanger, 2006). Several studies have demonstrated the application of LCA and LGMM in clinical trials to uncover important information about classes of responders and non-responders (Muthén and Brown, 2009; Wu et al., 2009; Gueorguieva et al., 2011; Muthén et al., 2011).

Given the mixed results from the main efficacy study on methamphetamine dependence (Elkashef et al., 2012), the present study was conducted to identify the heterogeneous treatment effect of topiramate and determine whether topiramate could reduce methamphetamine use effectively in a subgroup of subjects. To reach this goal, we applied both the LGMM and LCA approaches to the data from the trial reported by Elkashef et al. (2012) with the hope of identifying a subgroup of methamphetamine users with distinct trajectories who collectively showed significant improvement in the outcome measures of methamphetamine use. In turn, the identification of these distinct trajectories would provide a foundation for further development of biomarkers and other predictors of treatment response, as well as refinements in the design of methamphetamine clinical trials (Gueorguieva et al., 2011).

2. Methods

2.1. Description of the topiramate trial for methamphetamine dependence

As reported previously (Elkashef et al., 2012), this was a 13-week, multi-site, placebo-controlled, randomized trial of methamphetamine users who were 18–45 years old and met the *Diagnostic and Statistical Manual for Mental Disorders, 4th Edition* (DSM-IV; American Psychiatric Association, 1994) criteria for methamphetamine dependence. Prior to randomization, eligible subjects had to provide ≥1 methamphetamine-positive urine specimen (>500 ng/ml) during screening (days −28 to −15). Baseline measures over days −14 to −1 included ≥4 urine specimens, with one of them being collected from days −7 to −1. The test result from the last urine before randomization served as a predictor in the regression analysis. A total of 140 methamphetamine users from eight clinical centers were randomized to receive topiramate ($N = 69$) or placebo ($N = 71$). Starting at 25 mg/day, the dose of topiramate was escalated over the first 5 weeks of the trial until a daily dose of 200 mg/day or the subject's maximum tolerated dose was achieved. This dose was maintained over weeks 6–12 and tapered during week 13 for subjects to exit the study.

2.2. Outcome measures

The outcome measures in the main study were derived from methamphetamine use during the treatment period via self-reported substance use reports (SURs) and urine samples, which were collected from each participant three times per week (Elkashef et al., 2012). As there is no generally concise measure for clinically significant improvement in the treatment of methamphetamine dependence (Srisurapanont et al., 2001), we used both the primary and secondary outcomes from the main trial in the present investigation.

The primary outcome was weekly abstinence from methamphetamine (i.e., the negative use week) during weeks 6–12, the dosing maintenance period. A negative use week was any week in which all of the qualitative urine screens for methamphetamine were negative. Separately, weekly abstinence from methamphetamine during weeks 1–12 was considered as a longitudinal secondary outcome.

In addition, several binary indicators were defined as secondary outcome measures: (A) whether a subject could achieve 21 consecutive days of abstinence during which all urine drug screens were methamphetamine free, assuming that study days between urine specimens are methamphetamine free; (B) whether a subject could achieve 21 consecutive days of abstinence according to both urine samples and SURs; (C) whether a subject could decrease the proportion of methamphetamine use days according to SURs during the study period by at least 25% from the 14-day baseline period prior to randomization; (D) whether a subject could decrease the proportion of use days measured by SURs during the study period by at least 50% from the baseline; (E) whether a subject could decrease the median quantitative urine methamphetamine concentration during the study period by at least 25% from the baseline, and (F) whether a subject could decrease the median quantitative urine methamphetamine concentration during the study period by at least 50% from the baseline. As per the study protocol, study periods for these non-longitudinal secondary outcomes were weeks 6–12 for the period with a stable dose and weeks 1–12 for the entire treatment period, and the baseline period was days −14 to −1 before randomization.

2.3. Statistical analysis

We applied the latent growth mixture model (LGMM) to weekly abstinence from methamphetamine and latent class analysis (LCA) to non-longitudinal binary outcomes (McCutcheon, 1987; Muthén and Muthén, 1998–2010; Muthén et al., 2002; Keel et al., 2004). For the LGMM, the underlying heterogeneity was modeled by a categorical latent variable to represent distinct trajectories and a class-specific trajectory of methamphetamine non-use by a logistic growth model with random slopes. This model is similar to the alternative model described by Muthén et al. (2011). Subjects assigned to one group are more likely to share similar patterns of trajectories for methamphetamine use over time. The numbers of latent groups and growth parameters are specified a priori and estimated for each group, whereas group memberships are unknown but estimated using a multinomial logistic regression, accounting for the influence of topiramate and other covariates. Thus, the treatment effect of topiramate can be estimated from two points of view: its impact on the trajectory measure and that on class membership.

Several statistical criteria were used to determine the number of groups and model fit, mainly the Bayesian Information Criterion (BIC), sample-size adjusted BIC, entropy, and the Vuong–Lo–Mendell–Rubin adjusted likelihood ratio test (Muthén