Testing Mediators of Topiramate’s Effects on Alcohol Use Using Ecological Momentary Assessment Methods

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Conflict of Interest Disclosure

None
Overview

Guiding Questions

• How do medications facilitate behavior change in the treatment of alcohol misuse?

• How do we leverage technology and research methods to best answer this question?
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Today’s Presentation

• Review efficacy of topiramate (TPM)

• Review its putative mediators

• Present a study that used novel ways to test putative mediators

• Discuss the clinical implications
What is topiramate and how do we think it helps reduce alcohol use?

**Pharmacology**
- AMPA/kainite glutamate antagonist that facilitates GABA function

**Purported Mechanisms**
- Affects drinking via corticomesolimbic dopamine neurotransmission, which is tonically under GABAergic inhibitory control and glutamatergic excitatory control (Johnson et al. 2003)
- Inhibits dopamine release in the midbrain while drinking, thereby attenuating motivation (i.e., craving) to continue drinking (Johnson et al. 2003)
How efficacious is topiramate for treating alcoholism? (Blodgett et al., 2014)
What is known about how topiramate facilitates reductions in drinking?

Open-label trials

• Observed reductions in craving (Rubio et al., 2004; Paparrigopoulos et al., 2011)
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RCTs

- 6 trials examined craving
- Overall $g = .31$, $p = .07$ (Blodgett et al., 2014)
- Considerable heterogeneity among trials
- Self-efficacy (Kranzler et al., In press)

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Human laboratory paradigms

- TPM blunted the stimulant effects of alcohol (Miranda et al., 2008)
- TPM did not affect general craving or alcohol cue-induced craving (Miranda et al., 2008)
The Present Study

Overarching Goal
Identify mediators of TPM’s effects on drinking by pairing human laboratory and ecological momentary assessment (EMA) methods

- TPM decreases craving
- TPM blunts alcohol-induced stimulation & enhances sedation
- These effects mediate its effects on drinking
Study Design

Study Week | Dose (mg/day) | EMA
---|---|---
1 | 50 – 75 |
2 | 100 – 125 |
3 | 150 – 175 |
4 | 200 |
5 | 200 |
6 | 200 – 0 |

Focus of this Study

Titration Phase

Target Dose

Taper

Lab Paradigms

Alcohol Cue Reactivity

Alcohol Challenge
Participant Eligibility Criteria
Recruited from the community

Adults
- ≥ 18 years old

Nontreatment-Seeking
- Could not be seeking formal treatment beyond the interventions provided in a clinical trial in an academic medical setting

Heavy Drinkers
- ≥ 14 drinks/week/past 90 days (women)
- ≥ 18 drinks/week/past 90 days (men)
Our EMA Protocol

- Upon waking each morning
- After first 3 standard drinks
- Signal contingent every 3 to 6 hours
- Before first 3 standard drinks

Morning Reports

Random Reports

End Drink Reports

Begin Drink Reports

Random Reports

Begin Drink Reports

Before first 3 standard drinks

After first 3 standard drinks

Upon waking each morning
Momentary Assessments

EMA Reports

Random Reports
Begin Drink Reports
End Drink Reports

Craving
Single Item (0 – 10)

Stimulation
(Energized, Excited)

Sedation
(Sedated, Sluggish)
Data Stream for Three Participants
Data Stream for Three Participants

Target Dose: Focus of Analyses

Assessment Type
- Random Assessment
- Morning Report
- Drink Report (Begin or End)
## Participant Characteristics and Comparisons by Medication Condition

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Topiramate (n = 46)</th>
<th>Placebo (n = 50)</th>
<th>t or χ²</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>35.91 ± 12.04</td>
<td>35.74 ± 12.99</td>
<td>-0.68</td>
<td>.946</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>18 (39)</td>
<td>20 (40)</td>
<td>0.00</td>
<td>.931</td>
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<tr>
<td>Race (white)</td>
<td>33 (72)</td>
<td>36 (72)</td>
<td>3.39</td>
<td>0.640</td>
</tr>
<tr>
<td>Ethnicity (Hispanic)</td>
<td>5 (11)</td>
<td>7 (14)</td>
<td>0.25</td>
<td>0.616</td>
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<tr>
<td>Cigarette smoker</td>
<td>24 (52)</td>
<td>23 (46)</td>
<td>0.37</td>
<td>0.545</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>4 (9)</td>
<td>5 (10)</td>
<td>0.05</td>
<td>0.827</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>19 (41)</td>
<td>23 (46)</td>
<td>0.22</td>
<td>0.643</td>
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<tr>
<td>Drinks per drinking day</td>
<td>6.60 ± 3.26</td>
<td>7.18 ± 5.62</td>
<td>0.61</td>
<td>.543</td>
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<tr>
<td>Drinking days</td>
<td>73.23 ± 19.26</td>
<td>70.60 ± 21.70</td>
<td>-0.63</td>
<td>.533</td>
</tr>
<tr>
<td>Heavy drinking days</td>
<td>47.00 ± 27.76</td>
<td>45.16 ± 24.31</td>
<td>-0.34</td>
<td>0.732</td>
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</table>
**Effects of Topiramate on Alcohol Use at the Target Dose**

**Effects of TPM on the Likelihood of Drinking**

The unconditional main effect of condition showed no difference ($p = 0.69$).

The multivariate model including sex and baseline drinking levels suggested a marginal trend, OR = 0.63, 95%CI [0.37, 1.05], $p = 0.07$. 

![Bar chart showing percent drinking days for Placebo and Topiramate conditions](chart.png)
Effects of Topiramate on Alcohol Use at the Target Dose

Effects of TPM on the Average Number of Drinks Per Drinking Day

The TPM group consumed fewer drinks per drinking day, \( b = -1.35, 95\% \text{CI} [-2.62, -0.08], \text{SE} = 0.64, p = 0.03 \)

Effects remained significant when sex and baseline drinking levels were included in the model.
Predicting Momentary Subjective Responses to Alcohol from Medication Condition

in the model = 0). The pattern of results did not change when estimated blood alcohol concentration, sex, and baseline percent drinking days were added to the models.

*Miranda et al., Addict Biol, In press*
Interaction plot between medication condition and drinking moment on craving in the natural environment

Nondrinking moment refers to craving recorded in the natural environment during all momentary reports prior to drinking on a given day.

Drinking moment refers to craving recorded while drinking.

Miranda et al., Addict Biol, In press
Testing Mediation

Multilevel structural equation modeling with fixed slopes and Bayesian estimation method with diffuse (non-informative) priors
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Multilevel structural equation modeling with fixed slopes and Bayesian estimation method with diffuse (non-informative) priors

- **Dependent Variable**: # standard drinks/day (Week 5)
- **Independent Variables**
  - Medication condition
  - Craving (Week 5)
- **Control Variables**
  - # standard drinks/day (Week 4)
  - Craving (Week 4)
Rationale for Analytic Approach

Rationale for Statistical Approach

• Diffuse-prior Bayesian estimation is preferable to the likelihood approach when the distribution of the indirect effect parameter is skewed (Muthén, 2010)

• Using MLM, between- and within-subject effects are combined in estimating the indirect effect, which conflates the estimate (Preacher et al, 2010)
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Rationale for Focusing on Study Week 5

- Trial was designed to test effect of TPM at 200mg/day & that is where we found an effect on drinking
- Allowed TPM group to stabilize at the target dose
- Controlling for Week 4 measures allowed us to address the notion that changes in subjective responses at the target dose predict changes in drinking at the target dose
Results of Mediation Model for Craving

Note. Subjective Response to Alcohol = craving across drinking episodes; Drinking Outcome = # drinks per drinking day. Carryover effects of subjective response and drinking variables from study week 4 were controlled for in all models. The pattern of results did not change when sex and baseline drinking percent drinking levels were included.

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• Reduced daily quantities of alcohol use
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In terms of mediation…

• TPM reduced drinking indirectly by blunting alcohol-induced craving
What are the implications for clinical care?

Patient Care

- Help identify the types of people or circumstances best suited for particular medications
- Inform best ways to pair pharmacotherapy with psychosocial interventions
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• Help identify the types of people or circumstances best suited for particular medications
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Medication Development

• Inform best types and combinations of medications
• Inform ways to test new potential pharmacotherapies
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<td><strong>Advance Our Understanding of Addiction</strong></td>
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<td>• Refine our understanding of the processes</td>
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<td>that underlie pathological drinking</td>
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Next Steps

• Explore moderators (e.g., pharmacogenetics, age differences)
• Examine other putative mechanisms (e.g., inhibitory control)
• Test mechanisms in longer RCT
• Explore effects of alcohol and other drug co-use
• Use methods to identify other promising medications
• Identify the most important “mechanisms” that prospectively predict treatment outcomes
## Acknowledgements

<table>
<thead>
<tr>
<th>Role</th>
<th>Names</th>
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<tbody>
<tr>
<td>Collaborators</td>
<td>Chad Gwaltney, James MacKillop, Peter M. Monti, Damaris J. Rohsenow, Robert Swift, Jennifer W. Tidey, Hayley Treloar</td>
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<tr>
<td>Study Physicians</td>
<td>Thomas Chun, Robert Swift</td>
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<td>Project Staff</td>
<td>Alexander Blanchard, Shannon Carroll, Amy Christian, J.P. Massaro</td>
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<tr>
<td>EMA Programmer</td>
<td>Jason Frezza</td>
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<tr>
<td>Data Analysis</td>
<td>Hayley Treloar, Sue Sales</td>
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