Pharmacogenetics of Topiramate Treatment for Heavy Drinking

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Overview

- Introduction
- Pharmacology of topiramate
- Topiramate trials in alcohol use disorders
- Genetic moderation by a GRIK1 SNP
- Post-treatment effects
- Specificity of the moderator effect
- Self-efficacy as a mediator
Prevalence of Alcohol Use Disorders

NESARC: National Epidemiologic Survey on Alcohol and Related Conditions

- Any Alcohol Use Disorder: 17.6 million (8.5%)
  - Alcohol Abuse: 9.7 million (4.7%)
  - Alcohol Dependence: 7.9 million (3.8%)

Grant et al. 2004
Definitions

• **Moderation**: Interaction between a characteristic of the sample (e.g., genotype) and treatment, which identifies who responds best to treatment.

• **Mediation**: Causal link in the chain from treatment to outcome, which defines how the treatment exerts its effect.
Pharmacology of Topiramate

- Antagonist at AMPA and kainate receptors
- Allosteric agonist at the GABA-A receptor
- Blocks voltage-dependent Na and I-type voltage-gated Ca channels
- Inhibits carbonic anhydrase
- Enhances K+ conductance
Percent Change From Baseline at Week 12

- Heavy Drinking Days: Placebo (N=48) showed a decrease of 60%, while Topiramate (N=55) showed a decrease of 80%. The difference is statistically significant with a p-value of <.0004.

- Days Abstinent: Topiramate (N=55) showed an increase of 60%, while Placebo (N=48) showed an increase of 40%. The difference is statistically significant with a p-value of <.003.

Johnson et al., Lancet, 2003
Meta-analysis by Blodgett et al. (2014)
Identification of a Pharmacogenetic Candidate Variant

• Topiramate’s effects on glutamate (kainate) receptors are most potent and selective for those containing the GluK1 and GluK2 subunits.

• We examined 7 SNPs at intron-exon boundaries or other potentially functional sites in GRIK1, a large gene that encodes the GluK1 subunit.
Chromosome 21q21.3
## GRIK1 SNP Allele Frequencies for Self-identified EA Subjects

<table>
<thead>
<tr>
<th>SNP rs# Location</th>
<th>Allele 1</th>
<th>Controls (n=507)</th>
<th>CT AD (n=337)</th>
<th>MATCH AD (n=720)</th>
<th>All AD (n=1057)</th>
<th>p-value 2</th>
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<tbody>
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<td>rs2070398 31kb 3’</td>
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<td>0.796</td>
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Kranzler et al., Alcohol Clin Exp Res, 2009
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Kranzler et al., Alcohol Clin Exp Res, 2009
Rs2832407 Moderates the Severity of a Global Measure of Topiramate-induced Adverse Effects

Ray et al., 2009
Placebo-Controlled Trial of Topiramate to Reduce Heavy Drinking

- 12-week study of 138 heavy drinkers whose goal was to reduce drinking to safe levels
- Topiramate 100 mg twice daily (N=67) or matching placebo (N=71) with dosage increased gradually over 6 weeks
- Brief behavioral counseling at each visit
- Moderator analysis of rs2832407 in GRIK1

Kranzler et al., Am J Psychiatry, 2014
Study Design

Screening (n=200) → Baseline (n=138) → 12-Week Treatment
Topiramate (n=67; 82.1% completed tx)

12-Week Treatment
Placebo (n=71; 87.3% completed tx) →
3-month Follow-up
Topiramate (n=60; 90%)

3-month Follow-up
Placebo (n=63; 88.7%) →
6-month Follow-up
Topiramate (n=59; 88.1%)

3-month Follow-up
Placebo (n=59; 83.1%)

Kranzler et al., Alcohol Clin Exp Res, in press
Pretreatment Drinking Behavior: Mean (SEM)

Kranzler et al., Am J Psychiatry, 2014
Measures of Adherence

% Completing Tx

% IVR Calls

Topiramate

Placebo
Within-Treatment Heavy Drinking Days/Week

![Graph showing heavy drinking days per week vs. study week for Placebo Group and Topiramate Group.](image)
Within-Treatment Abstinent Days/Week

![Graph showing the number of abstinent days per week for two groups: Placebo Group and Topiramate Group. The graph displays the trend over study weeks.]
Genotype Groups

• We genotyped participants for rs2832407 in *GRIK1* as a moderator of topiramate’s adverse effects and effects on drinking behavior.

• The genotypes in European Americans (n=122) were in Hardy-Weinberg Equilibrium:
  - CC (n=51)
  - AC (n=53)
  - AA (n=18)

Kranzler et al., Am J Psychiatry, 2014
Adverse Events by Medication and Genotype Groups
Heavy Drinking Days by Medication and Genotype Groups

rs2832407

CC Genotype

AC Genotype

AA Genotype

Heavy Drinking Days Per Week

Study Week

Placebo Group  Topiramate Group
Abstinent Days by Medication and Genotype Groups

Figure: Main effect of medication group (A), and moderating effect of rs2832407 (B and C)
Validation of Self-Reported Drinking

GGTP

SIP Score

Kranzler et al., Am J Psychiatry, 2014

p=0.034

p=0.001
Pharmacogenetic Effects During Follow-up: PHDD

Kranzler et al., Alcohol Clin Exp Res, in press.

p=0.004
Summary of Effects on Drinking

• rs2832407 moderated the therapeutic response to topiramate
  – C-allele homozygotes significantly more responsive to topiramate than A-allele carriers
  – Effect persists beyond active treatment
  – Relevant to ~42% of European Americans

• Findings require replication and evaluation in other populations
Specificity of the Effects on Drinking

• We examined main effects of topiramate and moderation by rs2832407 on weight (BMI) in the subsample of EAs.

• The inclusion of study medication dosage level, antidepressant use, age, and heavy drinking days did not alter the results and none of the covariates uniquely predicted body weight.
Results

- No interaction of medication group x genotype group x study visit (p=0.51)
- Two-way interaction effect of medication group x study visit was highly significant (p<0.001).
  - For placebo, Δ = 0.0001 BMI units per visit (p=0.99)
  - For topiramate, Δ = 0.12 BMI units per visit (p<0.001). This translated to a 1.1 BMI unit decrease during the study
BMI by Medication Group by Visit

(mean change from baseline)

Study Visit
Summary

Rs2832407 moderated the therapeutic response to topiramate in heavy drinkers, but not its adverse effects or its effect on reducing BMI.
Micro-longitudinal Design

• Patients reported each evening via telephone on subjective effects and drinking over the preceding 24 hours. We focused on nighttime drinking following evening reports.

• Using medication effects with moderation by rs2832407 (CC vs. A-carrier), we examined whether confidence in avoiding heavy drinking (i.e., self-efficacy) mediated topiramate’s reduction of nighttime drinking.
Nighttime Drinking by Medication and Genotype Groups

- **C-Homozygotes**
  - Placebo
  - Topiramate

- **A-Carriers**
  - Placebo
  - Topiramate

**rs2832407 Genotype**

- Nighttime Number of Drinks
  - 0
  - 1
  - 2
  - 3
Confidence in Resisting Heavy Drinking

Confidence in Resisting Heavy Drinking

C-Homozygotes  A-Carriers

rs2832407 Genotype

Placebo  Topiramate
Self-Efficacy Mediates the Reduction in Drinking

A. C-Allele Homozygotes

\[ b = 1.16 \quad p < 0.001 \]

Self-Efficacy

\[ b = -0.65 \quad p = 0.001 \]

Medication Group

\[ b = -0.44 \quad p = 0.15 \]

Nighttime Drinking

B. A-Allele Carriers

\[ b = 0.04 \quad p = 0.85 \]

Self-Efficacy

\[ b = -1.01 \quad p < 0.001 \]

Medication Group

\[ b = 0.21 \quad p = 0.39 \]

Nighttime Drinking
Future Directions

• iPSCs may be a useful model to understand the effects on expression of rs2832407. The SNP is in nearly full LD with a SNP in the AS2 transcript in GRIK1, possibly explaining its functional effects.

• Perfusion fMRI may help to identify regional effects in brain of topiramate and rs2832407.

• Studies in populations other than EAs may help to elucidate the mechanism of effects of topiramate and rs2832407 on heavy drinking.
Personalized Treatment of AD

• A single SNP (rs2832407) may:
  • Identify individuals most likely to respond to topiramate (at least among EAs)
  • Mediation by self-efficacy suggests that CBT may augment the effects of topiramate
  • Provide a basis for enrichment trials of topiramate
  • Identify a key target for the development of more specific medications for alcohol treatment
Acknowledgments

• University of Connecticut Health Center: Jonathan Covault, Howard Tennen, Cheryl Oncken

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• Quinnipiac University: Richard Feinn

• Yale University: Joel Gelernter, Albert Arias

• University of Pennsylvania and Philadelphia VAMC: Timothy Pond, Kyle Kampman

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