Mediated Moderation Analysis of Topiramate for Treating AUD

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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

Within-Treatment Heavy Drinking Days/Week

Identification of a Pharmacogenetic Candidate Variant

- Topiramate’s effects on 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 on chr. 21q that encodes the GluK1 subunit.

### GRIK1 SNP allele frequencies for self-identified EA subjects

<table>
<thead>
<tr>
<th>SNP rs# Location</th>
<th>Allele</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</th>
<th>Haplotype Block #</th>
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<tr>
<td>rs2070398</td>
<td>C</td>
<td>0.783</td>
<td>0.796</td>
<td>0.805</td>
<td>0.803</td>
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<td></td>
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<td>rs2832387</td>
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**rs2832407**

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rs6516923

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<td>0.384</td>
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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
Within-Treatment Heavy Drinking Days by Medication and Genotype Groups

Pharmacogenetic Effects During Follow-up: PHDD

Kranzler et al., Alcohol Clin Exp Res, 2014
Summary

• rs2832407 moderated the therapeutic response to topiramate.
  ▪ Topiramate’s efficacy was significantly greater in the rs2832407*CC genotype group
  ▪ Relevant to ~42% of European Americans
  ▪ Effect persisted beyond active treatment

• Findings require replication and evaluation in other populations
Mediational Analysis

• To examine a potential mediator, we analyzed daily reports of drinking and confidence to resist heavy drinking using a micro-longitudinal design.

• Each evening, patients reported via telephone regarding the preceding 24 hours.

• We tested whether confidence in avoiding heavy drinking (i.e., self-efficacy) mediated topiramate’s reduction of nighttime drinking.

Kranzler et al., Addict Biol, 2016
Mediational Analysis

• A mediating role of mean self-efficacy would be shown by:
  – A significant Medication group × Genotype interaction in predicting nighttime drinking
  – A significant Medication group × Genotype interaction in predicting levels of self-efficacy
  – A reduction in the size of the effect of the Medication group × Genotype interaction in predicting nighttime drinking when mean self-efficacy level was included in the predictive equation

Kranzler et al., Addict Biol, 2016
Mediational Analysis

• To test the first two indicators of mediation, we used regression analyses to examine the interaction of the Medication group × Genotype interaction in predicting nighttime drinking and self-efficacy.

• Results showed that both outcomes were significantly predicted by the interaction.

Kranzler et al., Addict Biol, 2016
Nighttime Drinking by Medication and Genotype Groups

P = 0.001

P = 0.67

rs2832407 Genotype

Kranzler et al., Addict Biol, 2016
Confidence in Resisting Heavy Drinking

- **P < 0.001**
- **P = 0.77**

Kranzler et al., *Addict Biol*, 2016
Mediational Analysis

• We used MPLUS to test the indirect effect of the Medication group $\times$ Genotype interaction on nighttime drinking level through mean self-efficacy level.

• We estimated a 2-1-1 multilevel structural equation model with self-efficacy and drinking at level 1 (within subjects) and the medication group $\times$ genotype interaction at level 2 (between subjects).

• The indirect effect was the product of the between-subjects interaction effect on self-efficacy and the between-subjects self-efficacy effect on drinking.

Kranzler et al., *Addict Biol*, 2016
Self-Efficacy Mediates the Reduction in Drinking

Significant indirect effect of medication on drinking through self-efficacy for C-allele homozygotes, but not for A-allele carriers.
Implications for Personalized Treatment

• A SNP in GRIK1 (rs2832407) identifies EA heavy drinkers who are most likely to respond to topiramate.

• Mediation by self-efficacy raises a question as to whether a non-pharmacological treatment would augment the effects of topiramate or be an alternative to the medication in A-allele carriers.
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