Personalizing Topiramate Treatment for AUD

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• Consultant, Advisory Board Member, or CME Speaker: Alkermes, Lundbeck, and Otsuka

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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

Meta-analysis

**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*

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**Study Design**

- **Screening (n=200)**
- **Baseline (n=138)**
  - 12-Week Treatment Topiramate (n=67; 82.1% completed tx)
  - 3-month Follow-up Topiramate (n=60; 90%)
  - 6-month Follow-up Topiramate (n=59; 88.1%)
- **12-Week Treatment Placebo (n=71; 87.3% completed tx)**
- **3-month Follow-up Placebo (n=63; 88.7%)**
- **6-month Follow-up Placebo (n=59; 83.1%)**

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Within-Treatment Heavy Drinking Days/Week

Measures to Validate Self-Reported Drinking

GGTP

SIP Score

Kranzler et al., Am J Psychiatry, 2014
Pharmacogenetics

• Study of the genetic factors that underlie differences among individuals in their response to drugs:
  • Elucidate the mechanism of drug effects
  • Enhance clinical care by identifying moderators of adverse or therapeutic effects of medications
• Key component of personalized, precision, or stratified medicine

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>
</tr>
</thead>
<tbody>
<tr>
<td>rs2070398 31kb 3'</td>
<td>C</td>
<td>0.783</td>
<td>0.796</td>
<td>0.805</td>
<td>0.803</td>
<td>0.201</td>
<td>1</td>
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<tr>
<td></td>
<td>A</td>
<td>0.227</td>
<td>0.204</td>
<td>0.195</td>
<td>0.197</td>
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<tr>
<td>rs2832387 13kb 3'</td>
<td>G</td>
<td>0.667</td>
<td>0.722</td>
<td>0.712</td>
<td>0.715</td>
<td><strong>0.012</strong></td>
<td>1</td>
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<tr>
<td></td>
<td>A</td>
<td>0.333</td>
<td>0.278</td>
<td>0.288</td>
<td>0.285</td>
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<tr>
<td>rs2832390 intron 17</td>
<td>T</td>
<td>0.752</td>
<td>0.754</td>
<td>0.783</td>
<td>0.775</td>
<td>0.172</td>
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<tr>
<td></td>
<td>C</td>
<td>0.248</td>
<td>0.246</td>
<td>0.217</td>
<td>0.225</td>
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<tr>
<td>rs2186305 intron 17</td>
<td>A</td>
<td>0.664</td>
<td>0.678</td>
<td>0.714</td>
<td>0.707</td>
<td><strong>0.024</strong></td>
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<td></td>
<td>G</td>
<td>0.336</td>
<td>0.322</td>
<td>0.286</td>
<td>0.293</td>
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</tr>
<tr>
<td>rs363500 intron 15</td>
<td>G</td>
<td>0.727</td>
<td>0.735</td>
<td>0.759</td>
<td>0.754</td>
<td>0.132</td>
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<tr>
<td></td>
<td>A</td>
<td>0.273</td>
<td>0.265</td>
<td>0.241</td>
<td>0.246</td>
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<tr>
<td>rs2832407 intron 9</td>
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<td>0.612</td>
<td>0.668</td>
<td>0.658</td>
<td>0.661</td>
<td><strong>0.009</strong></td>
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<td>A</td>
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<tr>
<td>rs6516923 intron 7</td>
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<td>0.627</td>
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<td>0.384</td>
<td>0.376</td>
<td>0.373</td>
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</table>


**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)

Number Needed to Treat (NNT)

- NNT: number of patients who need to be treated to produce a positive treatment outcome relative to a control treatment
- Median NNT for major depression is 9 for TCAs and 7 for SSRIs
- Median NNT for AUD is 9 for both naltrexone and acamprosate
Adverse Event-Adjusted Number Needed to Treat (NNT-AE)

Number of patients who need to be treated to prevent one additional event without an additional adverse event. For the topiramate study:

- NNT to prevent any heavy drinking during the last month of treatment without an additional adverse event during the entire treatment period


<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo (n=30)</th>
<th>Topiramate (n=21)</th>
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</thead>
<tbody>
<tr>
<td>No HDDs</td>
<td>13%</td>
<td>57%</td>
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<tr>
<td>AE-Moderate</td>
<td>53%</td>
<td>67%</td>
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<tr>
<td>AE-Severe</td>
<td>3%</td>
<td>14%</td>
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<tr>
<td>NNT (95% CL)</td>
<td>2.28 (1.57, 5.71)</td>
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</tr>
<tr>
<td>NNT-AE Moderate</td>
<td></td>
<td>2.63</td>
</tr>
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</table>

### NNT and NNT-AE: AC or AA Genotypes (n=71)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo (n=36)</th>
<th>Topiramate (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No HDDs</td>
<td>19%</td>
<td>20%</td>
</tr>
<tr>
<td>AE-Moderate</td>
<td>53%</td>
<td>67%</td>
</tr>
<tr>
<td>AE-Severe</td>
<td>3%</td>
<td>20%</td>
</tr>
<tr>
<td>NNT (95% CL)</td>
<td>180.0 (5.22, -5.57)</td>
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<tr>
<td>NNT-AE Moderate</td>
<td>322.16</td>
<td></td>
</tr>
</tbody>
</table>


### Pharmacogenetic Effects During Follow-up: PHDD

Pharmacogenetic Effects During Follow-up: PHDD

Comparison of Acute and Chronic Dosing

Perez et al., unpublished

Two Ongoing and Two Upcoming Studies

- RCT with randomization stratified on genotype in EAs with AUD: Philadelphia, PA, USA (Kranzler)
- Selective GluK1 antagonist effects: extension to CPP and GRIK1 knockout models (De Biasi)
- RCT with randomization stratified on genotype in European ancestry individuals with AUD: Sydney, NSW, Australia (Haber)
- RCT in AA veterans; exploration of genetic moderators: Philadelphia, PA, USA (Oslin)
Summary: Implications for Personalized Treatment of AUD

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

• Findings argue for the use of enrichment trials of topiramate

• GluK1 may be a key target for the development of more specific medications for treating AUD.

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