Personalizing Topiramate Treatment for AUD

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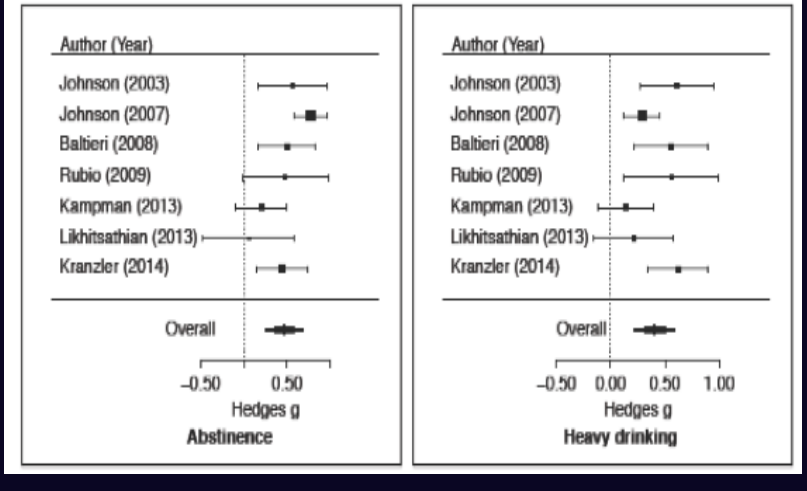
Pharmacology of Topiramate

- Antagonist at AMPA and kainate receptors
- Allosteric agonist at the GABA-A receptor
- Blocks voltage-dependent Na and l-type voltage-gated Ca channels
- Inhibits carbonic anhydrase
- Enhances K+ conductance

Meta-analysis



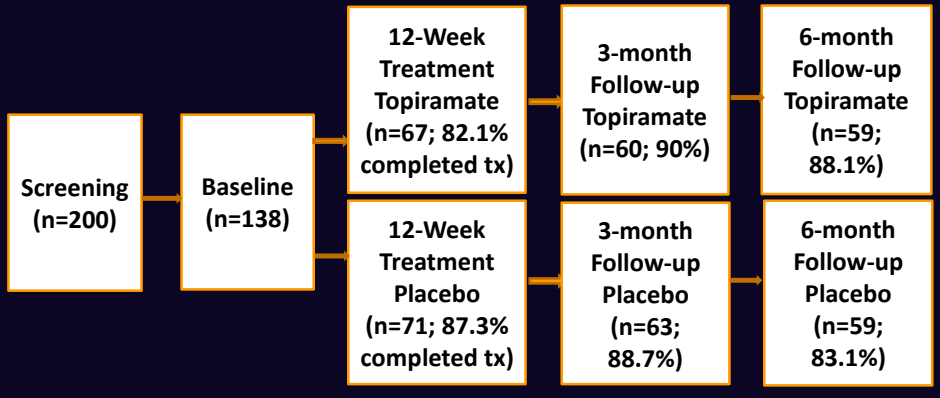
Blodgett et al., *Alcohol Clin Exp Res*, 2014

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*

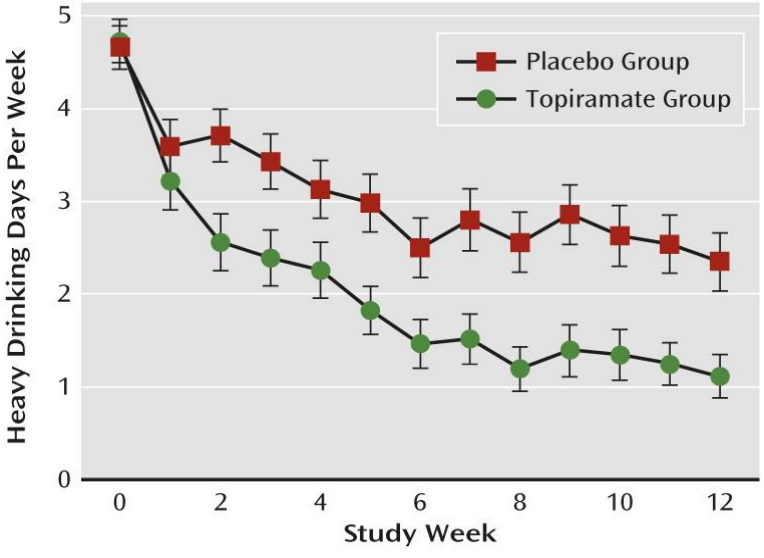
Kranzler et al., *Am J Psychiatry*, 2014

Study Design

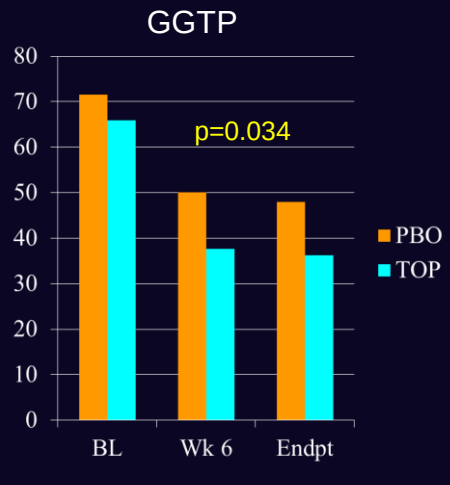


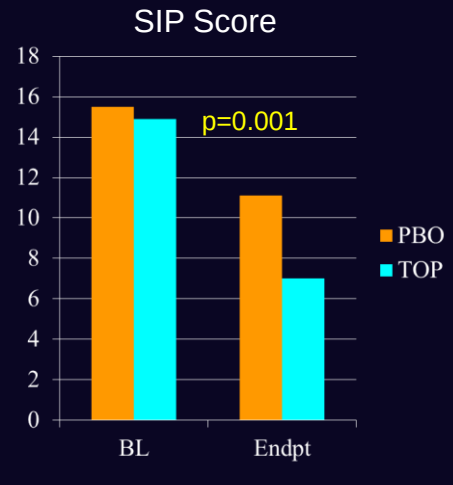
Kranzler et al., *Am J Psychiatry*, 2014

Within-Treatment Heavy Drinking Days/Week



Measures to Validate Self-Reported Drinking





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

SNP rs# Location	Allele [1]	Controls (n=507)	CT AD (n=337)	MATCH AD (n=720)	All AD [3] (n=1057)	*p*-value [2]	Haplotype Block #
rs2070398	C	0.783	0.796	0.805	0.803	0.201	1
31kb 3'	A	0.227	0.204	0.195	0.197		
rs2832387	G	0.667	0.722	0.712	0.715	**0.012**	1
13kb 3'	A	0.333	0.278	0.288	0.285		
rs2832390	T	0.752	0.754	0.783	0.775	0.172	2
intron 17	C	0.248	0.246	0.217	0.225		
rs2186305	A	0.664	0.678	0.714	0.707	**0.024**	2
intron 17	G	0.336	0.322	0.286	0.293		
rs363500	G	0.727	0.735	0.759	0.754	0.132	--
intron 15	A	0.273	0.265	0.241	0.246		
rs2832407	C	0.612	0.668	0.658	0.661	**0.009**	--
intron 9	A	0.388	0.340	0.341	0.339		
rs6516923	A	0.596	0.634	0.623	0.627	0.129	--
intron 7	T	0.404	0.384	0.376	0.373		

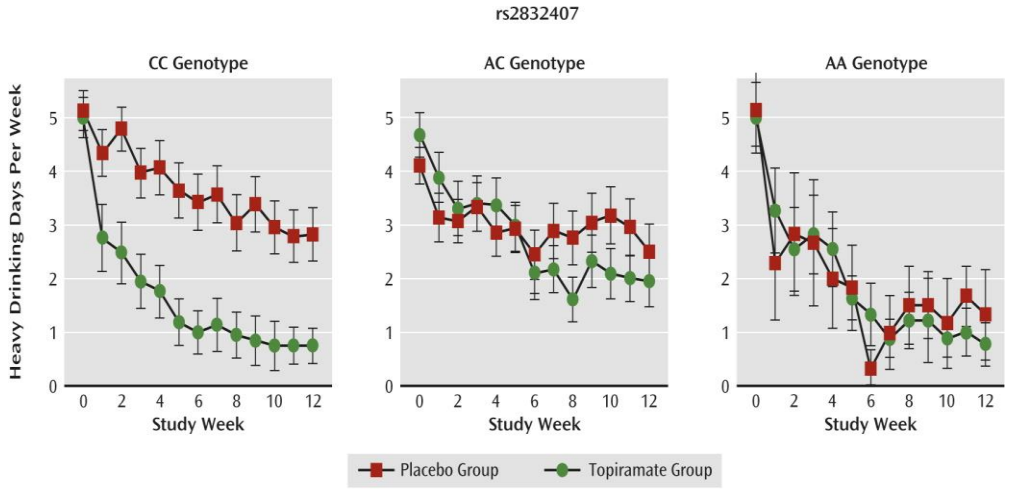
Kranzler et al., *Alcohol Clin Exp Res*, 2009

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

Heavy Drinking Days by Medication and Genotype Groups



Kranzler et al., *Am J Psychiatry*, 2014

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

Feinn et al., J *Clin Psychiatry*, 2016

NNT and NNT-AE: CC Genotype (n=51)

Measure	**Placebo (n=30)**	**Topiramate (n=21)**
No HDDs	13%	57%
AE-Moderate	53%	67%
AE-Severe	3%	14%
NNT (95% CL)	2.28 (1.57, 5.71)	
NNT-AE Moderate	2.63	

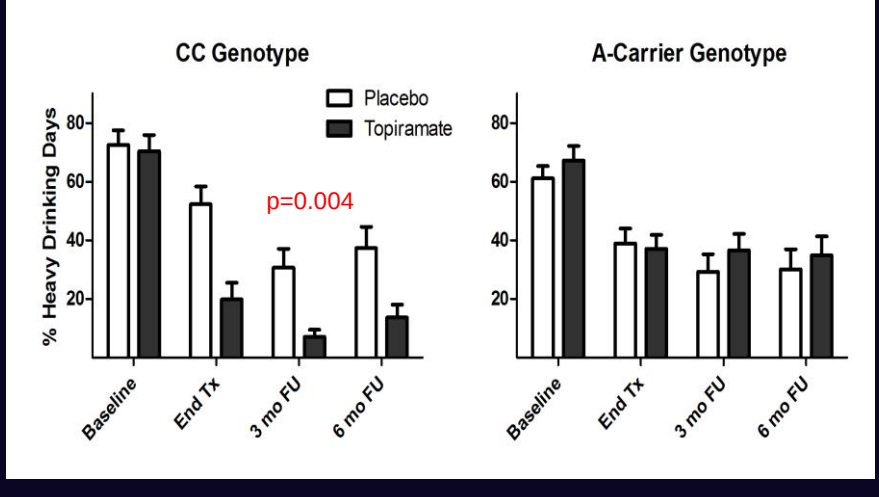
Feinn et al., *J Clin Psychiatry*, 2016

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

Measure	Placebo (n=36)	Topiramate (n=35)
No HDDs	19%	20%
AE-Moderate	53%	67%
AE-Severe	3%	20%
NNT (95% CL)	180.0 (5.22, -5.57)	
NNT-AE Moderate	322.16	

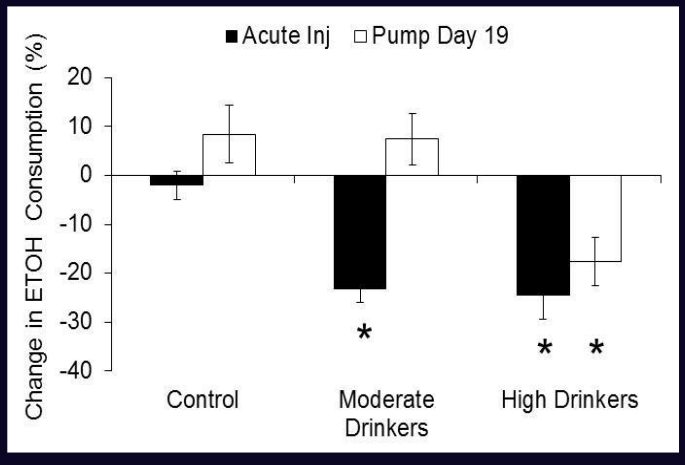
Feinn et al., *J Clin Psychiatry*, 2016

Pharmacogenetic Effects During Follow-up: PHDD



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

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 *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.

Acknowledgments

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