Personalizing the Treatment for Alcohol Use Disorders

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The Dr. Irving J. Taylor Professor and Chair of the Department of Psychiatry, Professor of Pharmacology and Professor of Anatomy & Neurobiology, Director of the Brain Science Research Consortium

Carter Memorial Lecture
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Duke University Hospital North

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Disclosures

• Professor Bankole A. Johnson is a consultant for the following companies:
  – D&A Pharma
  – ADial Pharmaceuticals, LLC (with which he also serves as Chairman)
  – Psychological Education Publishing Company (PEPCo), LLC

• Off-label medication use will be discussed in this presentation.

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Neuronal Pathways Associated with Alcoholism

Cortico-mesolimbic dopamine neurons are the principal neurocircuitry through which alcohol’s reinforcing effects associated with its abuse liability are expressed.

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Alcoholism is a Biological Disorder with a Moderate to High Heritability

Reasons for variability:
1. Race/ethnicity
2. Definition of phenotype
3. Sample size

Heritability:
Portion of trait variance attributed to genetic factors

Heritability estimate ($h^2$)

- Kalu 2012
- Ystrom 2011
- Knopik 2004
- Heath 1997
- Wilhelmson 2005
- Ehlers 2010
- Hansell 2008
- Walters 2002
- True 1999

Heritability estimates for various traits:
- Height
- Schizophrenia
- Bipolar Disorder
- Alcoholism

Heritability estimates are shown for different ancestries:
- African ancestry
- European ancestry
- Native American
- Mixed ancestry

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Genetic variants that alter neurotransmission, modulating the reinforcing effects of severe drinking, are promising biomarkers to personalize medications.

Pharmacogenetics

In alcoholism: The term is used for both the genetic modulation of psychotropic effects produced by the alcohol and the modulation of therapeutic effects produced by medications used for treatment (Heilig et al., 2011. *Nature Reviews Neuroscience*).

The goal: To find the right medicine for the right patient at the right time and for the right length of time (B.A. Johnson, personal communication).

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Serotonergic Pathways

- Serotonergic pathways that originate from the raphe nuclei and project to the cortex, hippocampus, and subcortical structures are an important mediator of drinking behaviors.

- These pathways modulate the function of cortico-mesolimbic dopamine neurons.

- Cortico-mesolimbic dopamine neurons are the principal neurocircuitry through which alcohol’s reinforcing effects associated with its abuse liability are expressed.

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The Serotonin Transporter and its Gene, SLC6A4

- The pre-synaptic serotonin transporter (5-HTT) gates 60% of neuronal serotonin function
- The gene encoding 5-HTTs, SLC6A4, is located on chromosome 17q11.1-q12
- Expression of 5-HTTs is determined by allelic differences in the SLC6A4 gene
- Allelic differences in SLC6A4 may be:
  - An important mediator of severe drinking behavior
  - A means of predicting treatment response in alcohol-dependent individuals to medicines that act at specific serotonergic receptor sites
- Alterations in platelet 5-HTT state associated with genetic variation can be a proxy for similar changes in neuronal cells

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L/S Alleles of 5'-HTTLPR

In Healthy Humans

- The homozygous LL variant, compared with the S allelic variant, is shown to have:
  - Higher transcription rates in lymphoblast cells
  - Greater 5-HT uptake into platelets and lymphoblasts
  - Increased binding of $[^{123}\text{I}]2\beta$-carboxymethoxy-3 $\beta$-(4-iodophenyl)tropane ($\beta$-CIT) in human raphe nuclei

- Hu et al. (2006) reported that 5'-HTTLPR is tri-allelic: the L allele with rs25531:G allele distribution was found to be associated with lower transcription rates similar to the 5'-HTTLPR:S allele

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L/S Alleles of 5'-HTTLPR (continued…)

In Alcoholics

- L-carriers, compared with SS-carriers, have:
  - Significantly less platelet 5-HT uptake
  - Reduced paroxetine binding capacity to platelet 5-HTTs

- Neuroimaging studies: Alcoholic 5'-HTTLPR:LL-carriers showed lower β-CIT binding to 5-HTT in the raphe nuclei brain areas, compared with non-alcoholics, suggesting an alcohol “toxicity” effect

- In alcohol-dependent L-carriers alone, the severity of lifetime drinking is associated with lower levels of 5-HT uptake and binding

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Research Study 1
– Biochemical Study 1

Hypothesis

Reduced binding or functional activity of the 5-HTT in L-carriers may be related to alcohol drinking

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Biochemical Study 1 Results (continued…)

- Platelet 5-HT uptake and binding parameters are significantly related to years of lifetime drinking for L-carriers but not the SS genotype.

- In L-carriers, a greater number of years of lifetime drinking is associated with lower uptake and binding for paroxetine (lower $K_d$).

- Platelet 5-HT and paroxetine binding parameters are significantly related to current drinking for L-carriers but not the SS genotype.

- In L-carriers, heavier current drinking is associated with greater uptake ($V_{max}$), lower binding ($B_{max}$), and reduced affinity (increased $K_m$) for 5-HT uptake.

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Regression coefficients (slopes) of platelet serotonin parameters ($\ln K_m$, $\ln V_{max}$, $\ln K_d$, and $\ln B_{max}$) on lifetime drinking:

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Platelet 5-HT uptake</th>
<th>Platelet paroxetine binding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$K_m$ vs. years of lifetime drinking</td>
<td>$V_{max}$ vs. years of lifetime drinking</td>
</tr>
<tr>
<td>L-carriers</td>
<td>-0.0160</td>
<td>-0.0214</td>
</tr>
<tr>
<td>p</td>
<td>0.0408</td>
<td>p&lt;0.0412</td>
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<tr>
<td>SS</td>
<td>0.0057</td>
<td>0.0019</td>
</tr>
<tr>
<td>b</td>
<td>0.683</td>
<td>0.920</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>0.01</td>
</tr>
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</table>

Regression coefficients (slopes) of platelet serotonin parameters ($\ln K_m$, $\ln V_{max}$, $\ln K_d$, and $\ln B_{max}$) on current drinking:

<table>
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<tr>
<th>Genotype</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$K_m$ vs. current drinking</td>
<td>$V_{max}$ vs. current drinking</td>
</tr>
<tr>
<td>L-carriers</td>
<td>0.0364</td>
<td>0.0466</td>
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<tr>
<td>p</td>
<td>0.0269</td>
<td>p=0.0351</td>
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<td>SS</td>
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<td>b</td>
<td>0.73</td>
<td>0.376</td>
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<td>p</td>
<td>0.07</td>
<td>0.06</td>
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Research Study 2
– Biochemical Study 2

Characterization of a Functional Polymorphism in the 3’ UTR of SLC6A4 and its Association With Drinking Intensity

Chamindi Seneviratne, Weihua Huang, Nassima Ait-Daoud, Ming D. Li, and Bankole A. Johnson

Hypothesis

The SLC6A4 single nucleotide polymorphism rs1042173 is associated with drinking intensity among treatment-seeking alcoholics

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Biochemical Study 2 - Methodology

• N = 275 Caucasian and Hispanic treatment-seeking alcoholics

• Transfect the 2 alleles (G/T) of rs1042173 into HeLa cell cultures

• Measured 5-HTT mRNA and protein expression levels using qRT-PCR and Western Blot
Expression vs. Drinks/Drinking Day

- mRNA expression in G-allele expressed cells
- mRNA expression in T-allele expressed cells
- Drinking severity (drinks/drinking day) in G-carriers
- Drinking severity (drinks/drinking day) in T-carriers

- $p < 0.0001$
- $p < 0.003$

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Biochemical Study 2 Conclusions

- Allelic variations of rs1042173 affect drinking intensity in alcoholics, possibly by altering transporter expression levels.

- Possible molecular mechanisms behind rs1042173 T/G specific alterations: miRNA binding, especially the T allele, is predicted to have higher affinity for several miRNAs (e.g., miRNA 15a, miRNA 135) compared with the G allele, increasing 5-HTT mRNA degradation.

- Together with 5'-HTTLPR, there are 2 functional polymorphisms of SLC6A4 associated with severe drinking.
Research Study 3
– Human Lab Study

Can Serotonin Transporter Genotype Predict Craving in Alcoholism?

Nassima Ait-Daoud, John D. Roache, Michael A. Dawes, Lei Liu, Xin-Qun Wang, Martin A. Javors, Chamindi Seneviratne, and Bankole A. Johnson

Hypothesis
5-HT transporter (5-HTT) polymorphism predicts craving in non-treatment-seeking alcoholics

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Human Lab Study
Methodology

• N = 34 Hispanic alcohol-dependent individuals

• Examine subjective and physiological cue craving for alcohol

• Determine whether there are differences in craving based upon genotype
rs1042173:TT genotype was associated with higher urge to drink ($p=0.002$) and crave for a drink ($p=0.005$) when exposed to alcohol cue. There was no difference within G-carriers.
Human Lab Study Conclusions

• L-carriers, versus their SS counterparts, have higher alcohol craving and possibly a higher propensity for drinking behavior

• Lower 5-HTT mRNA and protein expressing rs1042173:TT genotype was associated with greater cue-induced alcohol craving
Research Study 4
– Clinical Trial

Pharmacogenetic Approach at the Serotonin Transporter Gene as a Method of Reducing the Severity of Alcohol Drinking

Hypothesis
Allelic differences of SLC6A4 gene (5′-HTTLPR (L/S) and rs1042173 (G/T)) may mediate severity of drinking and predict therapeutic response to ondansetron, a 5-HT₃ receptor antagonist, in alcoholics

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John D. Roache, Ph.D.
Martin A. Javors, Ph.D.
Xin-Qun Wang, M.S.
Lei Liu, Ph.D.
J. Kim Penberthy, Ph.D.
Carlo C. DiClemente, Ph.D.
Ming D. Li, Ph.D.

*Am J Psychiatry 168:3, March 2011*

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Clinical Trial Methodology

• A controlled double-blind trial:
  – 283 alcoholics
  – Randomized by genotype (5'-HTTLPR:LL/LS/SS)
  – Further genotyping (rs1042173 (T/G))
  – Ondansetron (4 µg/kg twice daily) or placebo for 11 weeks
  – Weekly standardized cognitive behavioral therapy

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Individuals screened (N=657)

- Excluded (N=374)
  - Did not meet inclusion criteria (N=297)
  - Declined to participate (N=62)
  - Randomization failures (N=15)

Genotyped for 5'-HTTLPR alleles (N=283)

- Grouped into LL genotype (N=93)
  - Randomized to double-blind treatment (N=93)
    - Ondansetron (N=49)
      - Did not complete trial (N=17)
        - Limiting adverse event (N=1)
        - Participant choice (N=5)
        - Lost to follow-up (N=10)
        - Lack of efficacy (N=0)
        - Other (N=1)
      - Completed trial (N=32)
        - Included in intent-to-treat analysis (N=49)
    - Placebo (N=44)
      - Did not complete trial (N=17)
        - Limiting adverse event (N=1)
        - Participant choice (N=6)
        - Lost to follow-up (N=8)
        - Lack of efficacy (N=2)
        - Other (N=1)
      - Completed trial (N=27)
        - Included in intent-to-treat analysis (N=44)

- Grouped into S carriers (N=190)
  - Randomized to double-blind treatment (N=190)
    - Ondansetron (N=91)
      - Did not complete trial (N=33)
        - Limiting adverse event (N=1)
        - Participant choice (N=10)
        - Lost to follow-up (N=17)
        - Lack of efficacy (N=2)
        - Other (N=3)
      - Completed trial (N=58)
        - Included in intent-to-treat analysis (N=91)
    - Placebo (N=99)
      - Did not complete trial (N=25)
        - Limiting adverse event (N=4)
        - Participant choice (N=4)
        - Lost to follow-up (N=13)
        - Lack of efficacy (N=1)
        - Other (N=3)
      - Completed trial (N=74)
        - Included in intent-to-treat analysis (N=99)

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# Clinical Trial Baseline Demographics

<table>
<thead>
<tr>
<th>Measure b</th>
<th>Ondansetron (N=140)</th>
<th>Placebo (N=143)</th>
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<tr>
<td></td>
<td>LL (N=49)</td>
<td>LS/SS (N=91)</td>
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<tr>
<td>Age (years)</td>
<td>Mean</td>
<td>SD</td>
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<tr>
<td>Self-reported drinks per drinking day c</td>
<td>18.0</td>
<td>22.5</td>
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<tr>
<td>Self-reported percentage of days abstinent c</td>
<td>0.002</td>
<td>0.005</td>
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<tr>
<td>Breath alcohol concentration (%)</td>
<td>1.4</td>
<td>1.7</td>
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<td>Revised Clinical Institute Withdrawal Assessment for Alcohol scale score</td>
<td>30.8</td>
<td>12.0</td>
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<tr>
<td>Age at alcoholism onset (years)</td>
<td>25.0</td>
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<tr>
<td>Weight (kg)</td>
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<td>19.0</td>
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<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
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<tr>
<td>White</td>
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<td>77</td>
<td>81.9</td>
<td>37</td>
<td>88.1</td>
<td>81</td>
<td>86.2</td>
<td>37</td>
<td>84.1</td>
<td>81</td>
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<td>Hispanic</td>
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<td>8.2</td>
<td>14</td>
<td>14.9</td>
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<td>13</td>
<td>13.8</td>
<td>7</td>
<td>15.9</td>
<td>18</td>
<td>18.2</td>
<td>11</td>
<td>22.9</td>
<td>14</td>
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<td>Social class d</td>
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<td>1-3</td>
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<td>33</td>
<td>38.8</td>
<td>21</td>
<td>56.8</td>
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<td>43</td>
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<td>8.2</td>
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<td>2.7</td>
<td>7</td>
<td>8.1</td>
<td>3</td>
<td>7.5</td>
<td>5</td>
<td>5.8</td>
<td>2</td>
<td>4.9</td>
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</tr>
</tbody>
</table>

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Clinical Trial Results

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## Clinical Trial Effect Sizes

<table>
<thead>
<tr>
<th>Genetic Variant</th>
<th>Trait</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>5'-HTTLPR:LL</td>
<td>DDD</td>
<td>0.45</td>
</tr>
<tr>
<td>5'-HTTLPR:LL and rs1042173:TT</td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>5'-HTTLPR:LL</td>
<td>PDA</td>
<td>0.32</td>
</tr>
<tr>
<td>5'-HTTLPR:LL and rs1042173:TT</td>
<td></td>
<td>0.63</td>
</tr>
</tbody>
</table>

Effect sizes of 0.2, 0.5, and 0.8 are small, medium, and large, respectively.

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Clinical Trial Conclusions

- In the LL subjects, ondansetron was better than placebo at reducing drinks/drinking day (DDD)
- LL subjects, versus LS/SS subjects, had lower number of DDD
- 5'-HTTLPR and rs1042173 alleles interact significantly, and the LL/TT combination genotype best predicts treatment response to ondansetron
- mRNA transcription levels may predict therapeutic response to ondansetron
- 5-HTT genotypes are important in predicting drinking behavior
- 5-HTT genotypes can predict treatment response to ondansetron
  - 5'-HTTLPR:LL genotype has a small trending toward a medium effect on decreasing DDD
  - rs1042173:TT genotype has a small effect on decreasing DDD
  - 5'-HTTLPR:LL and rs1042173:TT combination has a medium trending toward a large effect on decreasing DDD

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Hypothesis

Ondansetron treatment response in alcoholics with the 5′-HTTLPR:LL genotype might have been mediated through specific regulatory effects of varying alcohol amounts on serotonin transporter (5-HTT) mRNA expression levels.

Therefore, 5-HTT mRNA expression levels in alcoholics carrying the 5′-HTTLPR:LL genotype might be a promising and novel biomarker to assess drinking severity in alcoholics quantitatively.
Study Procedure

Consented participants

Blood draw at baseline for 5'-HTTLPR genotyping and baseline 5-HTT mRNA expression

LL
N=14

Randomized to double-blind treatment

LL-OND
N=7

LL-Placebo
N=7

Week 4
Week 8
Week 12

LS/SS
N=27

LS/SS-OND
N=12

LS/SS-Placebo
N=15

Expression levels were correlated with drinking severity measured by drinks per drinking day (DDD) normalized to BMI

• Blood draw for 5-HTT mRNA expression
• Collection of self-reports on drinking amounts

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Expression Trends Within Each Treatment Group

Among ondansetron recipients:

- DDD/BMI had a significant interaction with 5'-HTTLPR genotypes \((p=0.0385)\)
- Ondansetron-treated LL subjects showed a positive correlation with DDD/BMI
- Ondansetron-treated LS/SS subjects did not show a correlation with DDD/BMI

Among placebo recipients:

- DDD/BMI did not have a significant interaction with 5'-HTTLPR genotypes \((p=0.7938)\).

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Expression Trends **Within Individuals** in Each Genotype Group Treated with Ondansetron

Each participant is represented by a single color

In each individual, increased drinking intensity increased mRNA expression levels

No clear pattern of mRNA expression level alterations with drinking intensity
Conclusions

The level of 5-HTT mRNA expression in subjects with the LL genotype is a promising genomic biomarker of drinking severity, and:

- It targets a pathophysiological mechanism in the brain associated with heavy drinking and thus may serve as a surrogate endpoint marker for severity of the disease itself
- Individual variability on serotonin transporter mRNA expression levels will be less as the mRNA is tested in a specific genotype group (5'-HTTLPR:LL)
- It can be tested in research or clinical facilities with access to a genetic laboratory
- Future studies in a controlled environment such as a human laboratory are necessary to validate the biomarker
Primary Drug Target of Ondansetron is $5\text{-HT}_3^A$ Subunit Encoded by $HTR3A$ Gene

$5\text{-HT}_3^A$ subunits form heterodimers with $5\text{-HT}_3^B$ subunits to form $5\text{-HT}_3^{AB}$ receptor complexes with higher signal transduction velocity than the $5\text{-HT}_3^A$ homodimers.

**Diagram:**
- Ondansetron
- Post-synaptic membrane
- $5\text{-HT}_3^{AB}$ receptor complex

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Research Study 6 –
Post-hoc Analysis of Ondansetron Clinical Trial Data to Test for Epistatic Effects of 5-HT$_{3AB}$ and 5'-HTTLPR Genetic Variations

Hypothesis
Prediction of ondansetron’s efficacy in reducing drinking severity is improved by combining the 5'-HTTLPR:LL and rs1042173:TT with putative functional polymorphisms in the $HTR3A$ and $HTR3B$ genes that encode the main target molecule of ondansetron (5-HT$_{3AB}$ receptor complex).
5-HT$_{3A}$ and 5-HT$_{3B}$ Subunits are Encoded by *HTR3A* and *HTR3B* Genes Located Next to Each Other on Chromosome 11
Pharmacogenetic Analysis Workflow in Ondansetron Trial

Selection of Genetic Variants

Screening

Filtering

Testing for Combined Effects

Genes encoding the primary target of ondansetron were selected as candidate genes. Polymorphisms within these genes were selected based on prior known functional variants, variants with previously known associations, and variants located in putative expression regulatory regions.

Screening parameter → Primary outcome measure across treatment period assessed for each genotype group in all 19 polymorphisms
Selection criteria: DDD reductions by ondansetron compared with placebo, within each genotype group:
   (1) >1.5 Standard drinks, and
   (2) p-Value <0.05, and
   (3) Sample size >5 individuals in each genotype x treatment group

Filtering parameter → Secondary outcome measures → PHDD and PDA across treatment period
Selection criteria: PHDD reductions and increased PDA by ondansetron compared with placebo, within each of the 6 genotype groups:
   (1) PHDD >10% and p-value <0.05, and
   (2) PDA >10% and p<0.05

Combined effects were tested on DDD, PHDD, and PDA using:
   (1) HTR3A and HTR3B genotype interactions
   (2) HTR3A and HTR3B genotypes and the previously reported two SLC6A4 genotype interactions

2 Candidate genes
HTR3A: 10 SNPs
HTR3B: 9 SNPs

4 Genotypes
HTR3A: 3 SNPs
HTR3B: 1 SNP

3 Genotypes
HTR3A: 2 SNPs
HTR3B: 1 SNP

4 Genotype combinations

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Genotype combination “rs1150226-AG, rs1176713-GG in \textit{HTR3A} and rs17614942-AC in \textit{HTR3B} (5-HT_3 combination)” predicted a significant difference between ondansetron and placebo

- had 2.50 fewer standard DDD during treatment
- had 20.58% lower PHDD during treatment
- had 18.18% higher PDA during treatment
- consisted of 23% of the study population
Subgrouping Based on “5-HT\textsubscript{3AB} Combination”
Improved Ondansetron’s Effect Size
from Small–Medium \(\rightarrow\) High

\(\theta = 0.867\) 
\(\theta = 0.780\) 
\(\theta = 0.683\)

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Research Study 6 - Results - 2

Genotype combination
“rs1150226-AG, rs1176713-GG in \textit{HTR3A} and rs17614942-AC in \textit{HTR3B} and 5'-H
tTLPR-LL, rs1042173-TT in SLC6A4
(5HT_{3AB}-5HTT combination)”
predicted a significant difference between ondansetron and placebo

- had 1.71 fewer standard DDD during treatment
- had 11.13\% lower PHDD during treatment
- had 11.57\% higher PDA during treatment
- consisted of 34\% of the study population

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Subgrouping Based on “5-HT_{3AB}–5-HTT Combination” Improved Ondansetron’s Effect Size from Small–Medium $\rightarrow$ Medium–High

Drinks/drinking day

<table>
<thead>
<tr>
<th>Genotype combination</th>
<th>Mean difference from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron</td>
<td>7</td>
</tr>
<tr>
<td>Placebo</td>
<td>4</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>5</td>
</tr>
<tr>
<td>Placebo</td>
<td>2</td>
</tr>
</tbody>
</table>

$\theta = 0.593$

Percent heavy drinking days

<table>
<thead>
<tr>
<th>Genotype combination</th>
<th>Mean difference from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron</td>
<td>6</td>
</tr>
<tr>
<td>Placebo</td>
<td>3</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>5</td>
</tr>
<tr>
<td>Placebo</td>
<td>2</td>
</tr>
</tbody>
</table>

$\theta = 0.416$

Percent days abstinent

<table>
<thead>
<tr>
<th>Genotype combination</th>
<th>Mean difference from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron</td>
<td>4</td>
</tr>
<tr>
<td>Placebo</td>
<td>1</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>3</td>
</tr>
<tr>
<td>Placebo</td>
<td>0</td>
</tr>
</tbody>
</table>

$\theta = 0.428$

Courtesy of Prof. B. Johnson. Please do not reproduce without permission.
The five genotypes (rs1150226-AG, rs1176713-GG in HTR3A and rs17614942-AC in HTR3B and 5'-HTTLPR-LL, rs1042173-TT in SLC6A4) can be combined as a 5-marker panel for a personalized treatment approach to alcohol dependence using ondansetron.

Courtesy of Prof. B. Johnson. Please do not reproduce without permission.
### Independent Validation of “5-HT\textsubscript{3AB}–5HTT Combination” with Generalized Multifactor Dimensionality Reduction (GMDR) Method

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Interaction Model</th>
<th>Test Accuracy</th>
<th>Cross-Validation Consistency (CVC)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDD</td>
<td>HTR3A: rs1176713–SLC6A4: 5'-HTTLPR</td>
<td>0.674</td>
<td>10/10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>HTR3A: rs1176713–SLC6A4: 5'-HTTLPR, rs1042173</td>
<td>0.595</td>
<td>10/10</td>
<td>0.039</td>
</tr>
<tr>
<td></td>
<td>HTR3A: rs1150226,rs1176713–HTR3B:rs17614942–SLC6A4: 5'-HTTLPR, rs1042173</td>
<td>0.483</td>
<td>10/10</td>
<td>0.576</td>
</tr>
<tr>
<td>PHDD</td>
<td>HTR3A: rs1176713–SLC6A4: 5'-HTTLPR</td>
<td>0.612</td>
<td>7/10</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>HTR3A: rs1176713–SLC6A4: 5'-HTTLPR, rs1042173</td>
<td>0.594</td>
<td>10/10</td>
<td>0.031</td>
</tr>
<tr>
<td></td>
<td>HTR3A: rs1150226,rs1176713–HTR3B:rs17614942–SLC6A4: 5'-HTTLPR, rs1042173</td>
<td>0.565</td>
<td>10/10</td>
<td>0.094</td>
</tr>
<tr>
<td>PDA</td>
<td>HTR3A: rs1176713–SLC6A4: 5'-HTTLPR</td>
<td>0.593</td>
<td>8/10</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>HTR3A: rs1176713–SLC6A4: 5'-HTTLPR, rs1042173</td>
<td>0.628</td>
<td>10/10</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>HTR3A: rs1150226-rs1176713–HTR3B:rs17614942–SLC6A4: 5'-HTTLPR, rs1042173</td>
<td>0.598</td>
<td>10/10</td>
<td>0.029</td>
</tr>
</tbody>
</table>

*Empirical P-values were generated with 1000 permutations.

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Conclusion

Tailoring pharmacological agents for subgroups of alcoholics based on their genetic variation may considerably improve treatments that otherwise produce small improvements.
Other Pharmacogenetic Findings from Recent Studies….

<table>
<thead>
<tr>
<th>Medication</th>
<th>Genetic variant</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naltrexone</td>
<td>OPRM1</td>
<td><strong>Greater efficacy in Asp40 allele subjects</strong> – Oslin et al. (Neuropsychopharmacology 2003;28:1546-52)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>No genotype effect</strong> – Gelernter et al. (Alcohol Clin Exp Res 2007;31:555-63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Greater efficacy in Asp40</strong> – Anton et al. (Arch Gen Psychiatry 2008;65:135-44)</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>5'-HTTLPR : L/S</td>
<td><strong>Significantly reduced drinking amounts in LL-carriers</strong> – Kenna et al. (Alcohol Clin Exp Res 2009;33:315-23)</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>GATA4 SNP rs13273672 : A/G</td>
<td><strong>A allele had higher abstinence levels</strong> – Kiefer et al. (Pharmacogenomics J 2011;11:368-74)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>DRD4 VNTR</td>
<td><strong>VNTR-L individuals showed greater reductions of craving</strong> – Hutchison et al. (Neuropsychopharmacology 2003;28:1882-8)</td>
</tr>
</tbody>
</table>

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Alcoholism Treatment Decision Tree
— Incorporating Personalized Treatment

Do you sometimes drink beer, wine, or other alcoholic beverages?

YES
Administer Questionnaire AUDIT

AUDIT score
Men: <8
Women: <4

AUDIT score
Men: ≥8
Women: ≥4

Excessive drinking

“Safe” limits
Men under 65: ≤4 standard drinks per day and ≤14 standard drinks per week
Women under 65: ≤3 standard drinks per day and ≤7 standard drinks per week
Men and Women over 65: ≤3 standard drinks per day and ≤7 standard drinks per week

Detailed questioning about drinking in the preceding 12 months

Any ABUSE symptoms
0–2

Any dependence symptoms according to DSM-IV criteria

0
1 or more
3 or more

NO DIAGNOSIS
ABUSE DIAGNOSIS
DEPENDENCE DIAGNOSIS

CURRENTLY DRINKING OR ABSTINENT

For treatment options, see next slide

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Alcoholism Treatment Decision Tree — Incorporating Personalized Treatment (Continued)…

DSM-IV-TR: Alcohol dependent

- Middle-aged patient
  - Liver function
    - Impaired
    - Non-impaired
      - A drug that is not metabolized in the liver
        - Currently drinking
          - Negotiate a drinking goal
        - Currently abstinent for at least 3–5 days
          - Supportive benzodiazepine to achieve 3–5 days of abstinence

- Emerging adult patient
  - Motivation-based behavioral therapy to:
    - Set treatment goals on reducing binge and heavy drinking episodes
    - Educate about health risks associated with alcoholism and risky behavior
  - Negotiate a drinking goal
  - Genetic testing
    - Carrier of:
      - SLC6A4-5HTTLPR:LL and rs1042173:TT, and/or HTR3A-rs1150226: AG, and/or HTR3A-rs1176713: GG, and/or HTR3B-rs17614942: AC
      - Not a carrier of the marker genotypes
        - Supportive benzodiazepine to achieve 3–5 days of abstinence
  - Elderly/isolated/forgetful patient with no major depression
    - Supportive benzodiazepine to achieve 3–5 days of abstinence

- TOPIRAMATE
- BACLOFEN
- ONDANSETRON
- NALTREXONE oral
- NALTREXONE extended release

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Overall Conclusions

- 6 Research Studies
  - Biochemical & Molecular Genetic Studies
    - 5-HTT alcohol-dependent L-carriers have less 5-HT uptake and binding
    - Show the effect of alcohol on gene expression based upon genotype
    - Allelic variations of rs1042173 affect drinking intensity in alcoholics
    - Show the effect of genotype on drinking intensity
    - Suggest that an alteration in transporter expression levels may be responsible
  - Human Laboratory Study
    - L-carriers have greater alcohol craving than their SS counterparts
  - Clinical Trial and Additional Analyses
    - Epistasis among HTR3A-rs1150226:AG and -rs1176713:GG; HTR3B-rs17614942:AC, and 5-HTT:LL/TT best predicts response to ondansetron
    - Show that genotype can predict treatment response
    - mRNA transcription levels may serve as a new biomarker to quantify drinking behavior

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Acknowledgments

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