Personalizing Smoking Cessation Pharmacotherapy using the Nicotine Metabolite Ratio

Neal L Benowitz MD

Professor of Medicine, University of California San Francisco
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Disclosure Statement

Dr. Benowitz consults with several pharmaceutical companies that market smoking cessation medications and has served as an expert witness in litigation against tobacco companies.
Why the Rate of Nicotine Metabolism is Important

- Determinant of how much people smoke and associated disease risks
- Determinant of level of nicotine dependence and response to smoking cessation treatment
Biology of Nicotine and Smoking Behavior

1. Tobacco Product
2. Environmental Influences
3. Smokin Behavior
4. Nicotine in Body
5. Nicotinic Cholinergic Receptors
6. Neurotransmitter Release
7. Reinforcement
   - Enhanced Performance
   - Mood Modulation
   - Lower Body Weight
   - Reversal of Withdrawal Symptoms
   - Self-Medication
8. Metabolism
9. Vulnerability Factors
   - Age
   - Gender
   - Genetics
   - Psychiatric Disease
   - Substance Abuse

Tolerance
Hypothesis Relating Variation in Nicotine Metabolism to Dependence

- Faster Nicotine Metabolism
- Shorter Nicotine Half-life
  - More Rapid and Intense Withdrawal Symptoms
  - More Frequent Self-Administration (Negative Reinforcement)
    - Higher Level of Dependence
    - More Difficulty Quitting
  - Faster Dissipation of Tolerance
    - Greater Response to Next Cigarette (Positive Reinforcement)
Nicotine Metabolism
Genotype is not enough: CYP2A6 Gene Variants and Nicotine Metabolism
CYP2A6 Variant Groups and Nicotine Metabolism

![Bar chart showing Cl Nic and Cl Nic → Cot (ml/min/kg) and Half life (min) across different genotype groups.](chart.png)
Frequency of CYP2A6 Activity Group Among Racial/Ethnic Population

- Japanese
- Korean
- Chinese
- African–American
- Caucasian

Nicotine metabolism group (%)
Factors that Influence Nicotine Metabolism

- Genetics
- Racial differences
- Sex hormones
- Pregnancy
- Drugs
- Food (grapefruit juice)
- Liver and kidney disease
A Non-Invasive Way to Assess CYP2A6 activity and the Rate of Nicotine Metabolism: the Nicotine Metabolite Ratio
Nicotine Metabolite Ratio

- Trans 3’hydroxycotinine/cotinine (3HC/COT)
- Can be measured in blood, saliva or urine of tobacco users
- Measure of CYP2A6 activity and clearance of nicotine
Nicotine Metabolism Pathways

Nicotine N-oxide → FMO

Nicotine → CYP2A6

Nicotine Δ(6) IMINIIUM ION → ALDEHYDE OXIDASE

Nortcotine → CYP2A6

Cotinine → CYP2A6

Cotinine 5'-Hydroxycotinine

Cotinine → CYP2A6

Trans-3'-Hydroxy-cotinine
Plasma Cotinine and 3HC Levels Track Together Over Time in a Smoker

Subject 651-003

3HC ng/ml

<table>
<thead>
<tr>
<th>Time</th>
<th>3HC ng/ml</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
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<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td></td>
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<tr>
<td>54</td>
<td></td>
</tr>
<tr>
<td>60</td>
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</table>
Nicotine Metabolite Ratio is a Measure of CYP2A6 Activity and Nicotine Metabolism

Figure 5: Nic-d2 Clearance vs Nic-d4 3OH/Cot ratio

$r = 0.82$
Evidence Linking CYP2A6 Activity to Nicotine Dependence (Tyndale)

- Slow metabolizers (SM) smoke fewer cigarettes per day
- SM protected against becoming a smoker
- SM quit smoking more easily
Nicotine Metabolite Predicts Efficacy of Transdermal Nicotine For Smoking Cessation

3-HC/Cot Ratio in Quartiles (Slow → Fast Metabolism)

% Quit

End of treatment
6-months

(Lerman, Clin Pharmacol Therap. 2006)
NMR Predicts Smoking Cessation with Placebo but not Bupropion

(Patterson, Clin Pharmacol Therap. 2008)
Use of the nicotine metabolite ratio as a genetically informed biomarker of response to nicotine patch or varenicline for smoking cessation: a randomised, double-blind placebo-controlled trial

Caryn Lerman, Robert A Schnoll, Larry W Hawk Jr, Paul Cinciripini, Tony P George, E Paul Wileyto, Gary E Swan, Neal I Benowitz, Daniel F Heitjan, Rachel F Tyndale, on behalf of the PGRN-PNAT Research Group*

Lancet Respir Med, 2015
The NMR as a Diagnostic Tool for Targeted Therapy for Smoking Cessation

NMR
3HC/COT
Hypothesis

• In normal metabolizers varenicline will be more effective for smoking cessation than nicotine patch
• In slow metabolizers varenicline and nicotine patch will be equally effective
Study Design

- NMR stratified
- Placebo controlled
- Randomized
- Varenicline – 12 weeks: 1 mg twice daily, quit date day 7
- Nicotine patch – 11 weeks: 21 mg (6 wk), 14 mg (2 wk), 7 mg (3 wk)
- Brief telephone counseling
SMs oversampled (NMR<0.31) for 1:1 ratio; Primary outcome 7-day point prevalence abstinence at EOT; secondary point prevalence abstinence at 6M, side effects, cost
CONSORT Diagram

11237 Telephone Assessment of Eligibility

8825 Excluded or Declined
  - Smoking rate
  - Psychiatric comorbidity and medications

2412 Attended In-person Eligibility Screen

1055 Excluded: including NMR selection

1246 ITT (Randomized & Achieved Pre-Quit Session)

408 Placebo
  PLA Patch/PLA Pill

  297 Retained at EOT
  89 Refused/Missed**
  22 Withdrawn**

  283 Retained at 6 Months
  96 Refused/Missed**
  29 Withdrawn**

  408 Analyzed

418 Patch
  Patch/PLA Pill

  325 Retained at EOT
  69 Refused/Missed**
  24 Withdrawn**

  300 Retained at 6 Months
  88 Refused/Missed**
  30 Withdrawn**

  418 Analyzed

420 Varenicline
  PLA Patch/Varenicline

  334 Retained at EOT
  69 Refused/Missed**
  17 Withdrawn**

  296 Retained at 6 Months
  101 Refused/Missed**
  23 Withdrawn**

  420 Analyzed
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>PLA</th>
<th>PATCH</th>
<th>VAR</th>
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</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>43</td>
<td>44</td>
<td>45</td>
</tr>
<tr>
<td>White (%)</td>
<td>55</td>
<td>56</td>
<td>55</td>
</tr>
<tr>
<td>Age, M(SD)</td>
<td>46 (11)</td>
<td>46 (11)</td>
<td>45 (12)</td>
</tr>
<tr>
<td>Cigs/day, M(SD)</td>
<td>18.5 (7.9)</td>
<td>18.0 (7.0)</td>
<td>17.5 (5.9)</td>
</tr>
<tr>
<td>FTND M(SD)</td>
<td>5.4 (2.0)</td>
<td>5.2 (1.9)</td>
<td>5.1 (2.0)</td>
</tr>
</tbody>
</table>

All P values for treatment differences >0.10
Quit Rates by Treatment Arm and NMR Group

ORR (NMR-by-treatment) = 0.96; CI = (1.11, 3.46); p = 0.02 (GEE logistic regression)

Clinical Relevance

Number needed to treat (NNT): patch vs. VAR

NMs: 26 vs. 4.9
SMs: 10.3 vs. 8.1
Secondary Outcomes

• NMR x treatment interaction for VAR (vs. PLA) shows greater summary side effects for SMs but not NMs (p=0.04). For individual side effects:
  In SMs, VAR led to increases in nausea (p=0.0003) and abnormal dreams (p=0.005)
  In NM, VAR led to increases in nausea (p=0.01), but decreases in irritability (p=0.001), anxiety (p=0.01), and attentional disturbance (p=0.01).
• No NMR x treatment effects on nicotine patch (vs. PLA) side effects.
• No NMR x treatment effects on nicotine withdrawal.
Study Limitations

- Few Hispanics or Asians
- Excluded for comorbid psychiatric illness
- Quit rates lower than in some prior studies
Conclusions

• Results support the clinical use of NMR as a biomarker to guide choice of therapy for smoking cessation

• For slow metabolizers, varenicline and TDN equally effective; TDN fewer side effects

• For normal metabolizers, varenicline superior to TDN

• Limitation: point of care testing not yet available
Retrospective Studies Support Association

Slow metabolizers based on the NMR biomarker achieve clinically significant benefit from patch; patch is ineffective for fast metabolizers.

Fast metabolizers based on the NMR achieve clinically significant benefit from bupropion; bupropion is ineffective for slow metabolizers.

Slow metabolizers benefit from nicotine patch
Fast metabolizers: benefit from non-nicotine medication

Lerman et al., *Clinical Pharmacology and Therapeutics*, 2006; Schnoll et al., *Pharmacology, Biochem and Behavior*, 2009; Patterson et al, *Clinical Pharmacology and Therapeutics*, 2008; Lerman et al., *CPT*, 2010