POS6 Bas-3: Urine or blood: does it matter how you calculate the nicotine metabolism ratio?

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Introduction:

- Quit rates with current smoking cessation medications are disappointing: interested quitters are still more likely to fail than to succeed
- Findings suggest that quit rates with cessation medications can be improved by personalising treatment choice using biomarkers
- The nicotine metabolite ratio—NMR—is a genetically-informed biomarker of nicotine clearance: essentially how quickly the body is able to metabolise (or "clear") nicotine from the body
    - NMR is calculated as the ratio of two nicotine metabolites: 3-hydroxycotinine (3-HC) and cotinine (COT)
- Using this ratio, smokers can be separated into groups based on how fast they metabolise nicotine, with the two main groups being "normal/fast" metabolisers and "slow" metabolisers
- Researchers have found that the NMR can significantly predict treatment outcome for smokers treated with pharmacotherapy
- In work to date, blood-derived NMR measures have been used to personalise treatment
- However, there are various reasons—pharmacologically and practically—why urine should be a superior fluid to use to calculate NMR
    - The concentration in urine at the time of voiding reflects a volume-weighted average exposure as the bladder acts as a holding reservoir and is therefore less susceptible to variability
    - Blood-derived NMR test-retest reliability has been found to be problematic
- Here we test the feasibility of using urine-derived NMR to inform personalised treatments

Method:

- Data for this study were drawn from two cessation trials
- Study 1: 59 daily smokers provided *both blood and urine samples* for NMR calculation
    - Data generated from this study were used to compare NMR value derived from blood from those derived from urine
- Study 2: 213 daily smokers provided *urine samples only* and were then randomised (open-label) to receive either patch or varenicline
    - Data from this study were used to compared outcomes of "normal/fast" metabolisers and "slow" metabolisers
- In both studies, each participants' NMR was determined via ultra-high performance liquid chromatography-tandem mass spectrometry using established assays

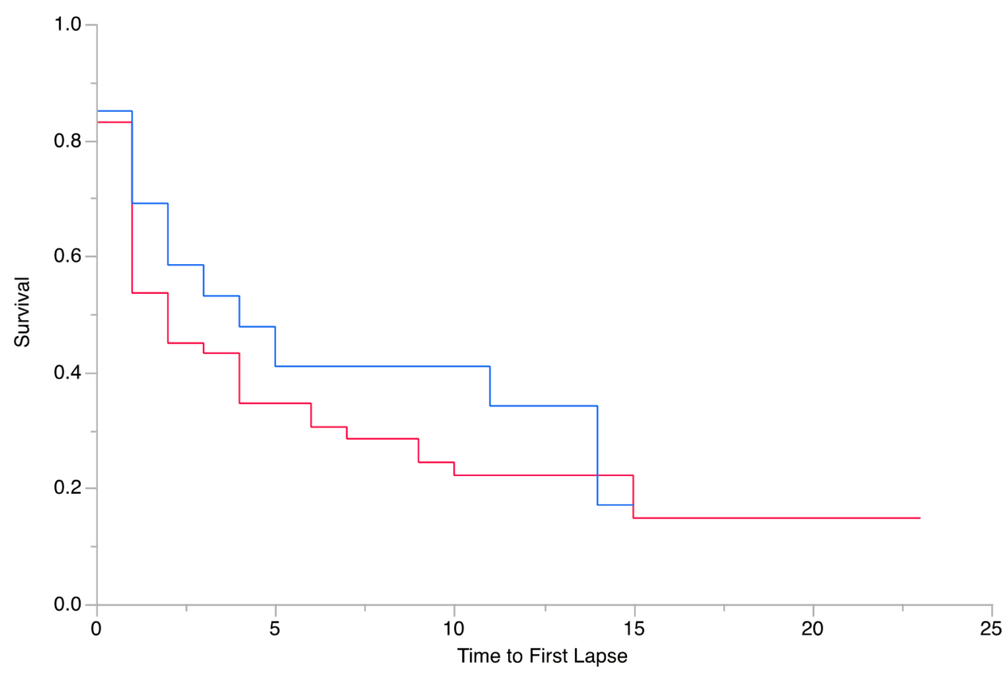

Figure: Time to first lapse for nicotine patches treatment group, stratified by NMR (red = normal metabolisers, blue = slow metabolisers).

Results – Study 1:

- Blood-derived NMR values were moderately positively correlated with urine-derived NMR values ($r=0.5$, $p<.001$)
- However, the classification (normal/fast vs slow metabolisers) of 16% of participants changed depending on whether we used their blood- or urine-derived NMR scores

Results – Study 2:

- Among varenicline users, normal/fast metabolisers (based on urine) appear to be slower to experience their first lapse
    - RR=1.79, 95% CI 0.77-3.89, p=.17 (compared to slow metabolisers)
- Among patch users, normal/fast metabolisers appeared to be faster to experience their first lapse
    - RR=0.82, 95% CI 0.44-1.46, p=.52 (compared to slow metabolisers; see Figure)

Discussions:

- Urine-derived NMR appears to differ from blood-derived NMR, potentially leading to misclassification of smokers as fast or slow metabolisers
    - Such misclassification would reduce the effectiveness of treatment tailoring
- Results from Study 2 suggest that urine-derived NMR may be an effective biomarker of treatment outcome
    - Results from this study were consistent with those from previous studies that utilised blood-derived NMR values
- For both pharmacologically and practically reasons, urine should be considered a superior fluid to use to calculate NMR
- Urine-derived NMR may be an effective biomarker of treatment outcome
- Additional studies should explore whether urine-derived measures of NMR can be successfully used to personalise treatment

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