Personalizing Smoking Cessation Pharmacotherapy Based on the Nicotine Metabolite Ratio (NMR): A Systematic Review

Okoli, CTC., PhD, MSN, MPH, RN[1,3]; **Anand, V.,** M.D[2].

[1]University of Kentucky College of Nursing [2] Brody School of Medicine, East Carolina University [3]Eastern State Hospital, Lexington, KY

OBJECTIVES

- The ratio of nicotine metabolites, 3' Hydroxicotinine (3HC)/cotinine (COT), commonly referred to as the nicotine metabolite ratio (NMR) is an important biomarker for CYP2A6 activity, which has high correlation to nicotine dependence.
- Moreover, the NMR may be a crucial biomarker to predict the efficacy of smoking cessation pharmacotherapy and guide personalized treatment.
- The purpose of this study was to review the extant literature for interventions that incorporate the use of NMR in determining the efficacy of smoking cessation pharmacotherapy.
- Specifically, we describe:
  a) Characteristics (i.e., sample, intervention components, NMR values) of each study and
  b) Smoking cessation outcomes by NMR status

Methods

- A comprehensive search of the PubMED database was conducted
- Key words for the search included combinations of Smoking cessation and Nicotine Metabolite Ratio and Quitting smoking and NMR
- The search was limited to:
  a) Studies that assessed interventions addressing smoking cessation NMR,
  b) Were quantitative
  c) Were not literature reviews or Meta-analyses
  d) In the English language
  e) Were published before March 2016 (references of selected articles were also examined for potentially relevant articles)
  f) Studies that were secondary analyses of a parent study were excluded. In such a case, only the parent study was included
- Of 429 studies initially retrieved, after removing duplicates and employing a histrionic search of relevant articles, 9 studies remained pertinent for our study (see Figure 1).

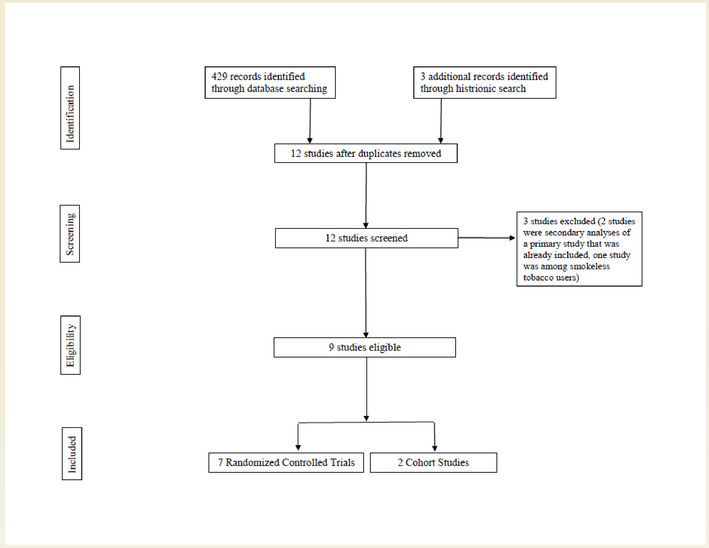

Figure 1. Flow Diagram of the Selection Process for Studies Included in the Review

Table 1. Sample Characteristics, Intervention Components, and Outcomes

Author (Year)	Population	Design, Time point	Treatment	Outcomes (significant p<.05, unless otherwise specified)
Lerman et al. (2006)	N=480 65% Caucasian, >10 cigs/day	RCT 6-month	Behavioral counseling plus either NP vs. Nasal spray	Greater SC among SM as compared to FM in NP group (29.6% vs 0.8%). No difference in SC by NMR in Nasal Spray group
Patterson et al. (2008)	N=414 82% European, cigs/day=21.5	RCT 6-month	BUP vs. Placebo	Greater SC among FM between BUP group and placebo group (27% vs. 8%). No difference in SC among SM between BUP group and placebo group (25% vs. 16%)
Schnoll et al. (2009)	N=568 84% Caucasian, >10 cigs/day	Cohort EOT (8wks)	Behavioral counseling plus 21mg NP	Greater SC among SM as compared to NM (42% vs. 28%)
Ho et al. (2009)	N=646 African American, ≤10 cigs/day	RCT 6-months	Self-help guide and behavioral counseling plus Nicotine gum vs. Placebo	Greater SC among SM group as compared to IMs/NMs (27% vs. 19%). Among females, SM group receiving NRT not significantly more likely to achieve cessation as compared to placebo.
Lerman et al. (2010)	N=471 Caucasian, cigs/day=22.1	RCT 6-, 12-months	NP (extended-6 months) vs. NP (standard-8 wks)	Greater SC among SM with extended therapy at 6- and 12-months
Chen et al. (2014)	N=709 European, ≥10cigs/day	RCT 3-month	Behavioral counseling plus BUP vs. NP and/or Lozenge vs. BUP + Lozenge	NP more effective in delaying relapse among FM as compared to SM. No effect of Bupropion on relapse delay by NMR
Lerman et al. (2015)	N=1246 Racially diverse, ≥10cigs/day	RCT 6- & 12-month	VAR vs. NP vs. Placebo	Greater SC with VAR as compared to NP among NM at 6- (22.0% vs. 13.6%) & 12- (16.0% vs. 13.1%) month. VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (14.1% vs. 19.4%) month.
Vaz et al. (2015)	N=662 Women, ≥10cigs/day	RCT At delivery	Behavioral counseling plus NRT vs. placebo	NMR was negatively associated with the odds of SC at delivery (OR=0.79; 95%CI=.066-0.95; p =0.010). Association unaffected by treatment assignment.
Kaufmann et al. (2015)	N=499 Racially diverse, ≥10cigs/day	Cohort EOT (8wks)	Behavioral counseling plus 8 weeks of 21 mg NP	Greater SC among SM as compared to FM (33% vs. 24%).

BUP=Bupropion, NP=Nicotine Patch, VAR=Varenicline, SM=slow metabolizer, NM=Normal Metabolizer, FM=Fast Metabolizer, IM=Intermediate Metabolizer, SC = Smoking Cessation, RCT = Randomized Controlled Trial, EOT = End of treatment

Results

- Five RCTs (Lerman et al., 2006; Patterson et al., 2008; Lerman et al., 2010; Chen et al., 2014; Lerman et al., 2015) and two Cohort studies (Schnoll et al., 2009; Kaufmann et al., 2015) found that NMR was significantly associated with the efficacy/effectiveness of smoking cessation pharmacotherapy (see Table 1).
- Studies which found no association between NMR and smoking cessation pharmacotherapy were among low African American Female cigarettes smokers (Ho et al., 2009) and pregnant and post partum women (Vaz et al., 2015)(see Table 1).
- In general, there was greater efficacy of nicotine replacement products in smoking cessation among slow metabolizers (lower NMR), whereas there was greater efficacy of smoking cessation with oral products (i.e., bupropion or varenicline) among fast metabolizers (see series of studies in Figure 2).

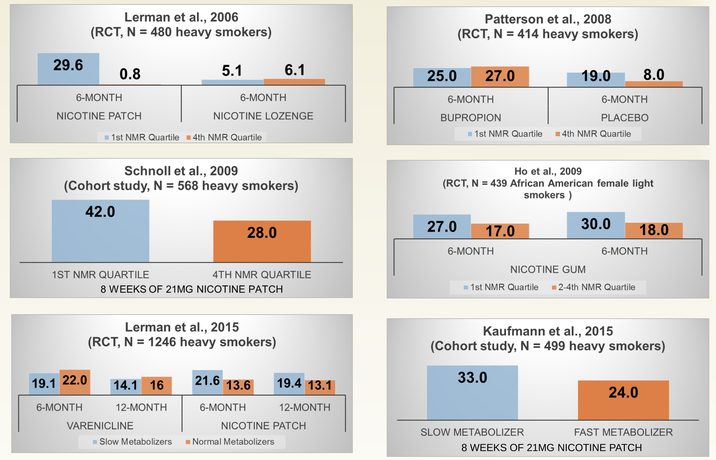

Figure 2. Selected Smoking Cessation Outcomes by NMR among Reviewed Studies

Conclusions

- The findings of this review suggest that the NMR is an important biomarker that can be used to personalize and optimize smoking cessation treatment.
- Future studies are needed to examine the outcomes of smoking cessation pharmacotherapy that is tailored to smokers based on NMR.
- Such studies will be instrumental in reducing the current disease burden associated with tobacco addiction.

For more information, please contact Chizimuzo T.C. Okoli: ctokol1@uky.edu