Pilot Study Investigating Rapid Visual Information Processing Task Assessment of Nicotine Delivery via Oral Nicotine Pouch Products

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Introduction

Lower-risk, non-combustible alternatives to cigarettes need to deliver sufficient nicotine in a manner that facilitates switching among adult smokers.[1-3] A challenge to developing potentially reduced harm tobacco products is the lack of objective, non-invasive, rapid measures of nicotine delivery. This pilot study explored whether cognitive task performance is sensitive to varying levels of nicotine via *on!*® nicotine pouches (NP) versus a nicotine-free oral pouch product.

Methods

Participants:
Adult Smokers (N=21; 11 Male, 10 Female) not interested in quitting smoking and with no prior NP experience who smoked an average of 10-20 cigs/day. Mean (SD) age of 36.9 (4.33) years.

Study Products:
Oral tobacco-derived NPs marketed as *on!*® Mint (designated "Test Products"; three nicotine levels: 2 mg, 4 mg, 8 mg nicotine/pouch)

Oral tobacco-free, nicotine-free pouches marketed as *Smokey Mountain*® Arctic Mint (designated "Control Product"; 0 mg nicotine/pouch)

Study Design:
We used a double-blind, randomized, crossover design to examine change in cognitive task performance following 15-minute use of flavor-matched oral pouches with and without nicotine. Participants completed six sessions: screening/consent, task familiarization/training, and four experimental sessions—varying only in nicotine level—following overnight abstinence from smoking. Abstinence was biochemically verified upon arrival to each session via expired-air carbon monoxide values ≤10 ppm.[4]

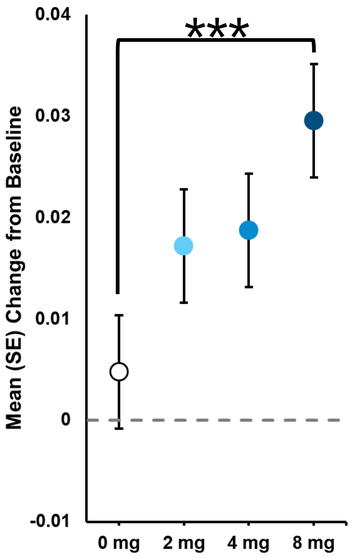
Experimental Session Procedures:
Cognitive assessment via the Rapid Visual Information Processing (RVIP) task[5] occurred at baseline and after that session's 15-minute use period of the assigned study product. The RVIP task, a validated measure of sustained attention,[6] was completed on a tablet computer, during which single digits appeared in a pseudo-random order at a rate of 100 digits per minute in a box in the center of the screen. During each seven-minute RVIP assessment, participants were tasked with detecting a series of three-digit target sequences (e.g., 3-5-7; 2-4-6; 4-6-8) and instructed to respond by touching a button at the bottom of the screen when they saw the final number of the sequence. Nine target sequences appeared every minute.

Rapid Visual Information Processing Task Outcomes:
Primary outcomes of interest include change from baseline (CFB) for Target Detection (A Prime) and Median Reaction Time (MRT) for correct responses. Raw scores for the Target Detection (A Prime) variable ranged 0.00-1.00, with higher scores indicating better performance. For MRT, lower values indicate better performance.

Results

Change from baseline (CFB) for each RVIP outcome was analyzed using a linear mixed-effects model via the Mixed Procedure in SAS. Each model included study product, randomization sequence, and numerical study day as fixed-model effects; subject was included as a random effect.

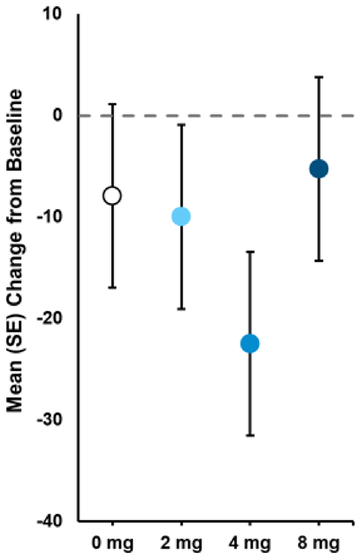
RVIP Target Detection (A Prime)



Target Detection (A Prime)
There was a statistically significant main effect of nicotine level on mean CFB, $F(3, 57) = 4.02$, $p = 0.01$. Each NP had a statistically significant increase (improved performance) from baseline, $t(57)$'s ≥ 3.07, p's ≤ 0.003. There was no significant change from baseline for 0 mg, $t(57) = 0.85$, $p = 0.40$.
Direct comparisons of NPs vs 0mg revealed statistically significant greater CFB (improved performance) for 8 mg, $t(57) = 3.46$, $p = 0.001$, but not for 4 mg or 2 mg, $t(57)$'s ≤ 1.94, p's ≥ 0.05.

Median Reaction Time
There was no significant main effect of nicotine level on mean CFB, $F(3, 57) = 0.82$, $p = 0.49$.

RVIP Median Reaction Time



Conclusion

Target detection showed sensitivity between nicotine- and non-nicotine oral pouches, with statistically significant improvement from baseline for each of the NPs, but not for the 0 mg pouch product. Comparing NP vs 0 mg pouches, the only statistically significant difference from 0 mg was observed at the highest nicotine level tested, 8 mg. Median reaction time was not sensitive to varying levels of nicotine. These results need to be interpreted in context of the limitations and strengths of the study. Participants completed the cognitive task 15 mins after initiating product use, which is less than the 30-45 mins needed to achieve maximum plasma nicotine from oral NP products. It is possible that greater differences among the nicotine levels tested here could occur with later assessment timepoints (i.e., ≥30 mins). Although the sample size of this pilot study was relatively small, use of a within-subjects design increased statistical power.[7] Further, testing acute nicotine administration via NPs among overnight abstinent smokers likely increased the robustness of the observed effects.[8] Additional studies among larger samples testing a wider range of nicotine levels and additional modalities of non-combusted nicotine delivery (e.g., heat-not-burn, e-vapor, etc.) are needed to establish the utility of this method or other models as non-invasive tools in the assessment of potentially reduced harm tobacco products.

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