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Greetings Colleagues,

What do you do when your patient who wants to quit nicotine accepts a prescription for NRT or varenicline and comes back in 6 weeks still smoking? Do you keep them on the same medication with a few behavioral tweaks? Do you add medication? Or something else? This study –punchline approaching -- suggests you switch them to varenicline if they are using NRT, or increase the dose of current therapy (if it is NRT or varenicline). Hallelujah – it is wonderful to have a novel approach, as well as evidence that is beyond that first step of treatment. The concept of dosing to effect is consistent with lessons learned over the years of treating OUD -and from that, we know that the dose of the blockade/replacement can make all the difference.

Here are the caveats. First, there was a loss to follow which probably doesn't but could lead to an overestimation of effect. Second, you'll note that this study excluded patients with substance use disorders (other than nicotine use do), so in addition to these higher doses being off-label, we cannot easily weigh the risks and benefits in our patients with SUD. In those with OUD, quit rates are so low that there is no evidence that medication helps at all, making an extrapolation to that group even less clear. Three, the benefits of a quit by twelve weeks were mostly gone by 6months. However, we know that it takes many quits for a sustained one, and all quits and returns to use are learning experiences that can set the stage for long-term improvement. So, despite the limitations, I think this data puts a new card up our sleeves for a difficult-to-treat use disorder.

Thank you for reading , details ahead...

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Title: Changing smoking cessation therapy through dose increase or switch from NRT to varenicline increases short-term quit rates.

Citation: : Cinciripini PM, Green CE, Shete S, et al. Smoking Cessation After Initial Treatment Failure With Varenicline or Nicotine Replacement: A Randomized Clinical Trial. JAMA. Published online May 02, 2024. doi:10.1001/jama.2024.4183

Link:<https://pubmed.ncbi.nlm.nih.gov/38696203/#:~:text=Conclusions%20and%20relavance%3A%20For%20individuals,and%20may%20be%20viable%20rescue>

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BACKGROUND

As the authors summarize, “Although one observational study reported increased abstinence from nicotine by increasing the varenicline dose to 3mg among those who had reduced but had not quit, another larger trial showed no such benefit.” And while a 21mg patch yields only 50% of the cotinine level of most smokers, higher dose patches are considered safe, but not necessarily more effective than 21mg. In this study, the investigators asked the question, when someone makes a nicotine quit attempt and does not succeed, what should the next medication step be?

METHODS

This was a double blind, placebo controlled trial involving a sequence of randomized assignments. In the initial 6wks (Phase 1), participants were randomized to usual dose varenicline versus combined nicotine replacement therapy (CNRT): 21mg nicotine-patch + 2mg lozenges ad lib. In wks 7-12 (Phase 2) those who were able to quit continued their therapy. Those who hadn't quit were 'rerandomized' to one of three conditions 1) Continue same therapy (representing usual care) 2) Switch therapy or 3) Increase dose. In this circumstance, **varenicline** was increased from 2mg daily to **3mg daily**, and the CNRT 21mg patch +2mg lozenges was increased to **two 21mg patches** + 2mg lozenges.

Participants were recruited from the Houston, TX area from 2015-2019. Included were those who smoked at least 6cigs/day with CO confirmation, were fluent in English and had stable housing and phone contact. Those with SUD, unstable psych disorders, mod-high suicidality scores, history of mania, current smoking treatments or CIs to study medications were excluded.

Interventions were as above with the following details: Participants were recommended at least 6 lozenges/day. The extra 1mg varenicline was given in the evening (ie, 1mg qam, 2mg qpm), and two 21mg patches were recommended to be applied at the same time, in the morning daily.

The primary outcome was 7day point prevalence (i.e., reported no smoking for the prior 7days with negative CO measures) and secondary outcome was continuous abstinence (i.e., 30days and 6months after target quit).

MAIN RESULTS

Population

Of 2232 initially interested, two thirds declined entry and ultimately, N=490 were initially randomized. Of the 490: 43% women; 58% non-Hispanic White, 26% non-Hispanic Af Am; mean age 48yrs; >73%employed; median education 13yrs; ~45% with income <50k/yr, average duration of smoking 28yrs; using avg 20cigarettes daily).

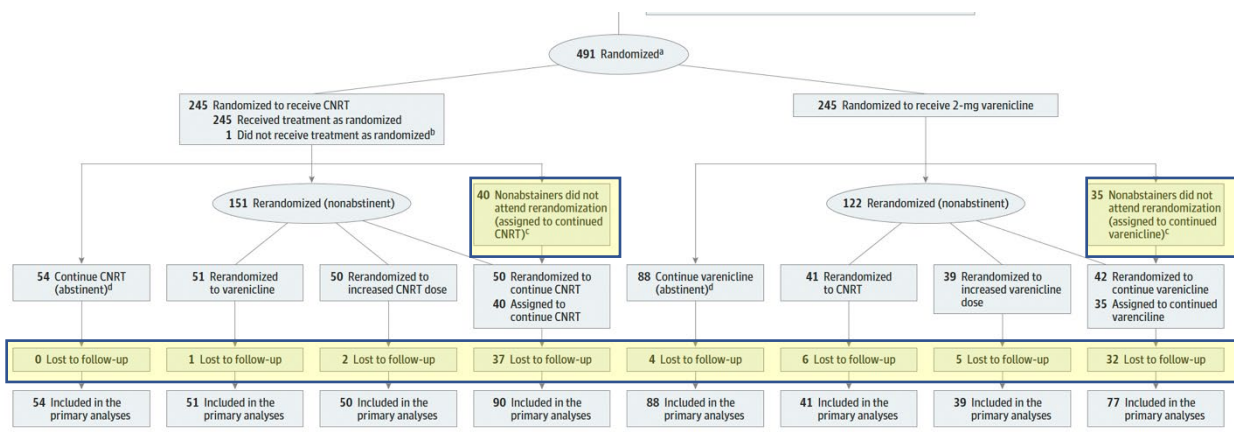
Phase 1 and Follow up Results

At the end of phase 1 (6wks), 22% (n=54) of CNRT were abstinent vs 36% (n=88) in varenicline. The absolute risk difference (RD) between the two treatments was -14% (95%CrI, -22%to -6%). (They didn't use p values but something else called Bayesian probability to say that there is a 99% change that this difference is non-zero).

191 (78%) in CNRT and 157 (64%) in varenicline did not abstain at 6wks. Of these, 78% were rerandomized. The other 22% did not attend the rerandomization. Of those n=40 (21%) were from Phase 1 CNRT and n=25 (16%) were from Phase 1 varenicline. These were assigned to the group that continued with their initial treatment.

Of those who abstained in Phase 1, 12 week follow up was 100% in CNRT and 95.5% in varenicline. Among those who did not initially abstain, completion was similarly high, except in the group assigned to continue, where 41% were lost, having included those who had not attended rerandomization at the end of Phase 1. Importantly, those lost to follow up were analyzed as non-abstinent.

Flowsheet depicting above:

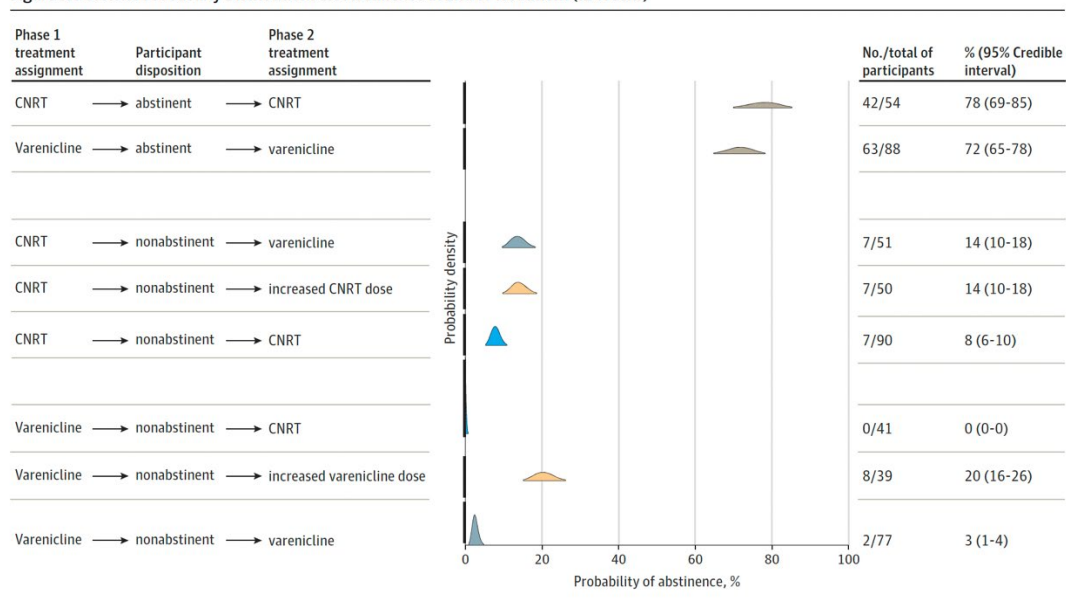


Phase 2 Results

Among initial non-abstainers in CNRT group, increasing dose or switch to varenicline had abstinence of 14%, compared with 8% in those who continued CNRT. The absolute risk difference for change vs continuation was 6% (95% CI 2-11%). **Among initial non-abstainers in the varenicline group, those who increased dose had 20% abstinence vs 3% for those who continued on the same dose vs 0% for those who switched to CNRT.** The absolute risk difference for switch to CNRT vs continue was -3% (95% CI, -4- -1%). Absolute risk difference for increasing dose of varenicline vs continuing was 18% (95% CI 13-24).

Among those who abstained initially, the rate of abstinence at 12 wks was 78% (69-85%). Figure 3 below shows these results in full.

Figure 3. Posterior Probability Distributions for Abstinence at End of Treatment (12 Weeks)



Looking at the secondary outcome of Continuous Abstinence, increasing the dose of either therapy was most successful but continuous abstinence rates among the initial non-abstainers were low, on the order of 0-8% for 30days post trial end and 0-3% at 6months. See ETable 9 below. Note that among phase 1 abstainers, 11% remained abstinent 30days post trial and 1% at 6months.

E-Table 9. Phase 2 Outcomes: Absolute Risk Difference (ARD) and 95% Credible Interval for the comparison of each rescue strategy (switch and increase) vs. continuation at each follow-up time point for continuous abstinence among non-abstainers at week 6 within the CNRT and Varenicline (VAR) phase 1 conditions

Phase 1 Treatment	CNRT		VAR	
Phase 1 Response	Non-abstainer		Non-abstainer	
Phase 2 Condition	VAR (switch)	CNRT+ (increase)	CNRT (switch)	VAR+ (increase)
Follow-up				
EOT+30*				
Continuous Abstinence ARD (95% CrI) Relative to Continue Condition**	6% (3%-10%)	5% (1%-8%)	0% (0%-0%)	8% (5%-11%)
6-months***				
Continuous Abstinence ARD (95% CrI) Relative to Continue Condition	1% (-2%-3%)	3% (0%-6%)	0% (0%-0%)	2% (1%-5%)

No serious adverse events were attributed to medication but **nausea** was more common in the varenicline group. (17% NRT and 54% varenicline). Of note, abnormal dreams were 35% in NRT and 38% in varenicline. No differences seen in depression (14-16%) or anxiety (10-11%). **Adherence to medication was high**, without large differences between pill (92%) or patch (77%). Lozenge use was variable in Phase 1 median of 40 (IQR 0-118) and Phase 2 76 (9.75-140).

CONCLUSION

If 6 weeks of the initial treatments with standard NRT or varenicline are not successful, increasing the dose of the present therapy or switching NRT to varenicline increases quit rates at 12 weeks among people without other SUDs or unstable psychiatric symptoms. Switching from varenicline to NRT reduces chance of quit. Long term abstinence was low, consistent with evidence about the nature of substance use disorders, and may be a part of the process of achieving a sustained quit.

COMMENTARY

This was an interesting and clinically relevant trial. It reinforced some non-head-to-head data that varenicline is more efficacious in the short term than NRT. It provided guidance about when to make a change if therapy is not working - as early as 6 weeks. It also provided guidance about what kind of change to make. It is fairly clear that moving from varenicline to NRT is not helpful but that moving from NRT to varenicline can be. It is also clear that increasing doses of each therapy can be helpful. Adverse effects of nausea are more common with varenicline (54 vs 17%), and may be limiting (*remember to have patients titrate up to target dose, and take with food*). Dreams and psychiatric events were no different between types of treatment in this select group. However, (there is always a however), there are a few validity considerations to keep in mind.

Internal validity (*Do the observed results represent the truth about the study group?*)

The patients lost to follow up were analyzed as being non-abstinent. This is the best assumption, but it is an assumption, and since loss to follow up was much higher in the non-abstainers who continued (41%) than the group who abstained (<5%) and other groups with quits, it could theoretically inflate the findings. (i.e., what if some of the folks who were lost to follow actually quit but were assumed not to quit). This is doubtful, though, as cessation is difficult, and generally, those who are doing well tend to continue in therapy.

External validity (*Can these results be applied beyond the study?*)

This study excluded people with SUDs and unstable psychiatric disorders. It was a relatively well-educated, highly employed, and housed group of individuals. And by

the nature of being enrolled in an RCT, they were likely more motivated to quit and to tolerate adverse effects such as nausea than in typical clinical practice. All of this may overestimate the effect of the intervention when applied to broader populations. The exclusion of folks with SUD is particularly limiting. It was likely done because the authors wanted to be able to detect a difference and there is evidence that standard pharmacotherapies do not improve quit rates in people with OUD¹. But this leaves a question about what we should do with our OUD patients, who almost universally use tobacco. In addition, this trial suggests safety but is not powered to detect rare outcomes. Finally, there is the practical question of whether insurance will cover these higher doses, which are presently off-label. Still, this seems like a nice addition to our repertoire. We've seen with buprenorphine and methadone that dosing matters and that may be in effect here – but I'd be sure to share with patients the above caveats of this off-label approach and the nascent nature of the findings.

REFERENCES

1. Vlad, C., Arnsten, J.H. & Nahvi, S. Achieving Smoking Cessation Among Persons with Opioid Use Disorder. *CNS Drugs* **34**, 367–387 (2020). <https://doi.org/10.1007/s40263-020-00701-z>