

UW-CTRI Triple Medication Smoking Cessation Study

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A. Study overview

The primary aim of *Transforming the Treatment of Tobacco Use in Health Care: Seizing the Potential of the Electronic Health Record to Deliver Comprehensive Chronic Care Treatment for Smoking* is to overcome barriers to effective treatment of smokers in the primary care setting. One of the major obstacles identified is the lack of treatment effectiveness. We believe that this lack of effectiveness is largely due to two factors. First, most treatments delivered in the healthcare setting are isolated applications of a single type of cessation treatment. Optimal chronic care for tobacco dependence requires multiple types of interventions that collectively target the different phase of quitting, are sustained over time, and are adaptive. A second factor contributing to the lack of treatment effectiveness is that translational science is not yet sufficiently powerful so as to make the most effective smoking interventions appropriate for, and effective in, real world healthcare contexts. The proposed R35 research is intended to address this deficit by developing and applying innovative, efficient, and powerful research methods to translate efficacious treatments into clinical use.

This study, the second in a series of studies being implemented as part of this NCI grant (R35CA197573), will focus on the treatment effectiveness obstacle by piloting a potentially more powerful combination of two of the most effective pharmacotherapies: varenicline plus combination nicotine replacement therapy (NRT) treatment. Data from this pilot study will help inform the design of future studies that would use this combination treatment as a cessation tool within the chronic care arsenal of treatments.

B. The rationale for combining varenicline and combination NRT

Smoking cessation medication is clearly effective, but there is room for substantial improvement. For instance, meta-analyses conducted for the 2008 PHS Guideline¹ showed that, generally, about three-quarters of smokers fail to achieve long-term abstinence when using FDA-approved smoking cessation pharmacotherapies. In fact, this level of effectiveness often declines in real world use (where smokers may be less motivated, adherent, and receive less counseling). Thus, despite effectiveness and high potential reach, evidence based smoking medications fail to help most smokers who use them achieve long-term abstinence.

Recent research suggests that a new combination therapy may be especially effective in increasing long-term abstinence from smoking. A study by Koegenlenberg et al. published in the *Journal of the American Medical Association*, showed that varenicline combined with the nicotine patch produced a remarkably high 6-month, 7-day point prevalence abstinence rate: i.e., 65.1% in the multiple imputation (MI) analyses, and 44% in the traditional intent-to-treat analyses². These rates were about 15-20 percentage points higher than those produced by varenicline alone (V: 46.7 and 28.8%, respectively for the MI and intent-to-treat analyses). The multiple imputation results are remarkable because it is so rare for a readily translatable smoking treatment to produce long-term abstinence in a clear majority of users. If this finding were replicated, this combination pharmacotherapy approach could become widely used and drive higher rates of smoking treatment delivery in healthcare.

Combinations of FDA-approved therapies have shown to have a reasonable safety profile. UW-CTRI has used combination NRT in multiple studies. In the most recent study for which a complete dataset is available, combination NRT (patch + lozenge) was evaluated in a sample of 1,086 participants. Commonly reported adverse events included itching or hives (18%), nausea (15%), and vivid dreams (13.4%) in the combination NRT group (n=421). Of note, among participants receiving the nicotine patch

alone (n=241), rates of vivid dreams and itching or hives were higher (17.5% and 23.1%, respectively), while rates of nausea were lower (8.7%), than in the combination NRT group. Participants in the same study who received varenicline alone (N=424) most often reported adverse events of nausea (30.4%), vivid dreams (24.6%), and insomnia (23.6%). There were two serious adverse events reported in this study: angioedema resulting in hospitalization (adjudicated as an allergic reaction to varenicline), and a stroke (adjudicated as possibly related to NRT use). Because there was some overlap in adverse events between those using combination NRT and those using varenicline, one might anticipate synergistic or additive effects. However, in the Koegelenberg et al. (2014) study, participants assigned to varenicline and nicotine patch differed significantly from participants assigned to varenicline and placebo patch only in their report of “any skin reactions” (14.4% vs. 7.8%, $p=.03$). Frequently reported adverse events for varenicline and nicotine patch included nausea (27.3%), insomnia (19.9%), and abnormal dreams (4.6%) – all at rates lower than reported in the UW-CTRI study using varenicline alone. This study also reported a total of seven serious adverse events. One was adjudicated as possibly related to study medication (pregnancy with trisomy 21 and associated congenital heart defects). One anembryonic pregnancy was adjudicated as unrelated; the other five SAEs were adjudicated as unrelated and not specified. The results from the Ebbert et al. (2009)³ report (the only other peer-reviewed publication reporting safety data for varenicline combined with NRT) are more difficult to interpret. This was a retrospective report of patients who had enrolled in a residential tobacco treatment program (rather than volunteer research participants); patients were not randomly assigned to treatment regimens, and were not in their typical environments. Of the 104 patients using varenicline and nicotine patch in this report 71% used an average nicotine patch dose of 32 mg/day (vs. 21 mg/day in the UW-CTRI and 15 mg/day in the Koegelenberg et al. studies). Up to 32% of the Ebbert et al. sample used two or three NRT products in addition to nicotine patch plus varenicline. As with the previous two samples, the most common adverse events reported with varenicline and NRT were insomnia (14%), nausea (13%), and vivid/disturbing dreams (12%).

A key purpose of the proposed study is to examine what types of tolerability concerns, if any, emerge and the timing of those events, in order to better assess how the use of this combination of tobacco cessation medicines can be most effectively delivered and monitored.

C. Detailed study protocol

Participants (n=40) will be recruited via Facebook ads contextually tagged to appear only to adults in the Madison, WI, area who have “liked” or posted about smoking. Those who click the ad will be taken to a Web page containing a brief description of the study and the opportunity to provide their contact information if they would like to learn more about the study.

Those persons who provide contact information will be called by study staff and provided with a more detailed description of what study participation would involve (time, risks, benefits, etc.). They will also be given an opportunity to ask questions. If they remain interested based on the description, study staff will proceed to assess inclusion/exclusion criteria for potential participants by way of a structured computer-assisted telephone interview. Participants who meet criteria will be invited to schedule an initial study visit. Those who do not meet criteria will be asked if they would like information about other smoking cessation treatment resources; if so, they will be given contact information for the Wisconsin Tobacco QuitLine.

Inclusion/Exclusion Criteria

Inclusion criteria will be: age >17 years; >=5 cigarettes/day for the previous 6 months; alveolar CO >= 6 ppm; able to read, write and speak English; planning to remain in the intervention catchment area for at least 4 months; not currently taking bupropion or varenicline; if the participant is currently using NRT, s/he agrees to use only study medication for the duration of the study; free of medical contraindications to NRT and varenicline; and, if participant is a woman of childbearing potential, using an approved method of birth control during treatment. Exclusion criteria will be: current diagnosis of/treatment for psychosis or bipolar disorder; suicidal ideation within the past 12 months; any history of suicide attempts; significant hepatic or renal impairment; history of significant allergic reactions to varenicline or any type of NRT in the past; use of any investigational drugs in the previous 30 days.

At the initial study visit, potential participants will review a Powerpoint presentation with a study staff member providing detailed information about study procedures, time commitment, risks, and benefits. They will also be given the IRB-approved Informed Consent Document and allowed to take as much time as they like to read it (including the option to take it home and return at a later date). They will be given the opportunity during both the presentation and reading of the ICD to ask questions. If they choose to provide written informed consent for study participation, staff will reconfirm all inclusion/exclusion criteria, including a CO breath test. Upon reconfirmation of study eligibility, participants will be asked to complete the surveys about nicotine dependence and withdrawal, smoking history and use of noncombustible tobacco products (see Assessment schedule below).

Each participant will be evaluated medically by a study physician, based upon inclusion/exclusion criteria, baseline assessments, and physical examination, as to their fitness for combination therapy. If a participant is determined to be medically appropriate, they will be provided with the following **medication regimen**:

1. Varenicline 0.5 mg once daily for three days; followed by 0.5 mg twice daily for four days; followed by 1 mg twice daily for 11 weeks.
2. Transdermal Nicotine 21 mg for eight weeks (starting on the Target Quit Date); followed by transdermal nicotine 14 mg for two weeks; followed by transdermal nicotine 7 mg for two weeks (Note: for participants smoking 5-9 cigarettes/day at baseline, the regimen will be 14 mg/day for 10 weeks followed by 7 mg/day for 2 weeks).
3. Nicotine mini lozenges (2 mg) to be used as needed for relief of withdrawal and craving, for 12 weeks starting on the Target Quit Date. Participants will be urged to use at least four mini lozenges per day, but no more than 20 per day.

All medicines will be provided in FDA-approved dosing in the manufacturer's original packaging. Precautions related to taking the medication will be reviewed by a study physician.

In addition to the medication regimen, all participants will be provided with a single individual smoking cessation counseling provided by Dr. Fiore and trained research staff, as per the United States Public Health Service *Clinical Practice Guideline: Treating Tobacco Use and Dependence*. Participants will also be asked to access a Web-based cessation support program (www.smokefree.gov). Target Quit Date (TQD) for all participants will be set for eight days from initiation of medication to allow for normal up-titration of varenicline.

Follow-Up

All participants will be followed over the 13 week course of treatment with structured assessment of safety, tolerability, treatment adherence, smoking, use of noncombustible nicotine, and treatment satisfaction. Participants will be contacted by a study physician during the week following their TQD to perform an AE assessment. This AE assessment screens for critical indicators of potential risks related to study medication, including cardiac problems and suicide ideation. Should any questions on the screener be endorsed as unresolved symptoms, a study physician will contact the participant to further discuss the symptoms, study medication use and other related personal or medical information. All other assessments (including additional AE assessments) will be weekly telephone calls conducted by study staff utilizing structured instruments shown in the Assessment Table below (MN Withdrawal Scale, noncombustible use assessment, timeline follow-back and adverse event assessment), with reports of adverse events being followed to resolution. Attribution of AE relatedness to study treatment will be made by Dr. Fiore. All AE assessments indicating unresolved symptoms which may be related to study medication will be assessed to determine any dosage adjustment (modification of dose or discontinuation of a medication.) Any Serious Adverse Events requiring reporting will be reported during mandated timeframes to the UW Health Sciences IRB and the National Cancer Institute (study sponsor).

Follow-up assessments will be conducted by telephone on a weekly basis, starting on the TQD and for four weeks thereafter (the period during which adverse events are most likely to emerge), then every two weeks for the following eight weeks. In addition to the structured assessment, study staff will also use a timeline follow-back procedure to track and smoking and noncombustible nicotine use on a daily basis during the treatment period, as these may influence treatment tolerability and efficacy assessments. Table 1 presents the study assessment schedule. In addition to the formal study assessments, participants will be able to initiate contact with study staff if they have questions/concerns regarding their treatment. Study staff will review follow-up data on a weekly basis. UW-CTRI's standing Data Safety and Monitoring Board will review overall study data after the first 5 participants have completed their first week post-quit; after the first 20 participants have reached that milestone; and at the completion of the study. [The DSMB comprises Drs. James Cleary, Burke Richmond, and James Sosman, all of whom are independent of the pilot study.]

Analytic plan

This is an exploratory study of the tolerability and feasibility of combining varenicline with combination NRT. There is no comparison group, so no inferential statistical tests are proposed. Data regarding safety will be summarized in descriptive tables based on the adverse event organ system and reported frequency. Should any Serious Adverse Events occur, they will be captured in a narrative manner, including the PI's assessment of relatedness to study medication. Participant-reported outcomes related to treatment acceptance and impact on withdrawal will be summarized and reported tabularly with mean and standard deviation for each item. Number of participants discontinuing any medication will also be summarized across the sample.

Given that no inferential statistical tests will be performed for this single-group, open-label, descriptive pilot study, it is not appropriate to provide a statistical power analysis. The sample size of 40 was selected to provide demographic diversity in terms of gender, socioeconomic status, and smoking history variables, as well as providing robust estimates of the incidence of possible adverse events related to the combination pharmacotherapy.

Data collection and security

Confidentiality of participant data and information will be accomplished by using participant numbers as unique identifiers, allowing us to keep participant data separate from identifying information. Data generated through study participant and data obtained on medical history from participants will be stored in secure databases under protections and procedures consistent with the guidelines and regulations of the UW School of Medicine and Public Health (UW-SMPH). Outside access is available only via an encrypted connection to the Department of Medicine Citrix server located at the UW Clinical Science Center in Madison. The servers at the University of Wisconsin Center for Tobacco Research and Intervention (UW-CTRI) Madison office are physically secured in a locked room. Data backups are created nightly and stored in a locked safe. Significant safeguards have been implemented to protect data including virus and adware protection, firewall, access controls and encryption when appropriate such as wireless and remote access. All UW-CTRI staff members have completed HIPAA/human subjects training and are aware of the sensitivity of study-related data. The UW SMPH has developed school-wide data security policies and procedures and these were implemented in 2009. UW-CTRI data security policies and procedures conform to those of the SMPH. UW-CTRI will use an enterprise-level database that supports audit trails such as access, change logging, and more sophisticated access control for managing and tracking user access privileges. No publications or presentations resulting from this research program will contain any identifying information about individual participants. All data including phone screen and study participant data will be prepared for analysis by eliminating all HIPAA identifiers and, within 9 months following the time the primary analysis, the study database will be archived and the study will be closed to IRB. Only the de-identified data set will be available for any future use, either by UW Investigators or others who may request data in accord with NIH guidelines.

Payment/retention plan

Participants will be compensated \$50 for attending the single in-person visit and \$10 for their time for completion of each telephone follow-up assessment following their initial visit, for a potential total reimbursement of \$140. All study medication and the initial assessments and smoking cessation counseling will be provided at no cost to participants.

Assessment schedule

	Wk -1	TQD	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
	Visit 1	Call 1	Call 2	Call 3	Call 4	Call 5	Call 6	Call 7	Call 8	Call 9
Smoking History	X									
Fagerstrom Test of Nicotine Dependence	X									
WI Index of Smoking Dependence Motives	X									
MN Nicotine Withdrawal Scale	X	X	X	X	X	X	X	X	X	X
Noncombustible Use Assessment	X	X	X	X	X	X	X	X	X	X
Timeline Follow-Back		X	X	X	X	X	X	X	X	X
Combination Treatment Assessment		X	X	X	X	X	X	X	X	X
Adverse Experience Assessment		X	X	X	X	X	X	X	X	X

References

1. Fiore MC, Jaen CR, Baker TB, et al. *Treating Tobacco Use and Dependence: 2008 Update*. Clinical Practice Guideline. Rockville, MD: US Department of Health and Human Services. Public Health Service. May 2008.
2. Koegelenberg C. F. N., Bateman E. D., van Zyl-Smit R. N., Bruning A., O'Brien J. A., Smith C., Abdool-Gaffar M. S., Emanuel S., Esterhuizen T. M., Iruken E. M. Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: a randomized clinical trial. *Journal of the American Medical Association*, 2014;312(2):155-161. doi:10.1001/jama.2014.7195
3. Ebbert JO, Burke MV, Hays JT, Hurt RD. Combination treatment with varenicline and nicotine replacement therapy. *Nicotine & Tobacco Research*. 2009;11(5):572-576.