Deep rTMS and Varenicline for Smoking Cessation:

A Pilot Study Exploring the Efficacy of a Combined Treatment Approach

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Address of Trial Site:

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Introduction

While first-line pharmacotherapies for nicotine dependence (i.e. varenicline) demonstrate efficacy for short term smoking cessation, relapse remains a challenge in smokers. Growing evidence implicates the insula in cigarette craving and cue-induced relapse, with studies showing improved abstinence rates following deep repetitive transcranial magnetic stimulation to this region. The present proposal aims to optimize smoking cessation outcomes in a generalizable group of smokers by combining currently approved pharmacotherapy (varenicline) with deep repetitive transcranial magnetic stimulation (rTMS), a novel therapeutic intervention with recently evidenced efficacy for smoking abstinence. Such a combined approach may improve abstinence rates in smokers through the synergistic action of these two separate interventions, targeting both cessation and relapse.

Background and Rationale

Although currently available pharmacotherapies for nicotine dependence have evidenced considerable efficacy in short term smoking outcomes, randomized trials reveal nearly three quarters of initial quitters relapse within a year [1, 2]. The risk for smoking relapse [3] and unsuccessful quit rates following pharmacotherapy treatment [4] are even higher among certain subgroups of smokers who are largely excluded from clinical trials (i.e., those with psychiatric and/or substance use co-morbidity) [5]. While varenicline demonstrates superiority over other first-line medications for smoking cessation [6], the probability of smoking relapse signals a clear need for improvement [7]. Indeed, novel multifaceted treatment approaches which in combination successfully address both cessation and relapse prevention are required to treat this complex disorder.

Varenicline: a novel therapeutic approach for smokers: The nicotinic acetylcholine receptors (nAChRs).are ligand-gated ion channels composed of five subunits, labeled α_2 to α_{10} and β_2 to β_4 in the central nervous system. The combination of subunits determines the functionality of the receptor. In the brain, the most prevalent of these are the homo-oligomeric α_7 and the heteromeric $\alpha_4\beta_2$ nAChRs. A large body of evidence implicates $\alpha_4\beta_2$ nAChRs in the reinforcing effects of nicotine [8-10]. Notably, the $\alpha_4\beta_2$ nicotinic acetylcholine receptors located in the midbrain area are critical for nicotine's ability to increase DA levels in the nucleus accumbens [11-15], an important factor linked to the motivational and reinforcing properties of drugs of abuse [16]. Recently, a partial agonist of the α4β2 nAChRs (varenicline), approved as a smoking cessation aid, has become available [17,18]. Varenicline has high affinity for $\alpha_4\beta_2$ (K_i $\alpha_4\beta_2$ = 0.4 nM) and much less for other human nAChRs (K_i α_7 = 125 nM; K_i $\alpha_3\beta_4$ = 86 nM; K_i $\alpha_{6/}$ $\alpha_3\beta_4$ = 111 nM) [19]. The rationale to develop partial agonist for smoking cessation was to have a duality of effect: acting as an antagonist to block the rewarding/reinforcing effect of nicotine while smoking; acting as an agonist to attenuate withdrawal and cravings due to abstinence [20]. By correlating free human brain concentrations, estimated from therapeutic human plasma levels and rat brain-to-plasma ratios, with binding affinities and functional potencies at $\alpha_4\beta_2$ nAChRs, Rollema *et al.* found that concentrations equal to predicted human brain concentration of varenicline can extensively desensitize and to a lesser extent activate $\alpha_4\beta_2$ in vitro [19], but minimal effect at α_7 nAChRs is expected [19]. Therefore, it is likely that the effects of varenicline in humans are mediated by $\alpha_4\beta_2$ nAChRs [19].

Repeated Transcranial Magnetic Stimulation (rTMS) as an innovative approach: rTMS is a technique that has been found to be useful as a potential treatment for neuropsychiatric diseases. rTMS is almost painless, does not require anesthesia, and is not associated with significant side effects. There is compelling evidence that rTMS works by affecting the function of neuronal circuits and inducing local changes in neural excitability. Transient inactivation of a specific brain structure can also be induced in humans through rTMS, through mechanisms that are likely associated with potentiation of $GABA_B$ receptor mediated inhibitory neurotransmission [21]. However, rTMS effects are complex and likely involve local modifications in the dynamic release patterns of various neurotransmitters, including dopamine [22-26]. The fact that there is *in vivo* evidence that rTMS of frontal brain regions has a modulatory effect on dopaminergic system, suggest that rTMS may be particularly useful in neuropsychiatric disorders associated with dopamine dysfunction, such as addiction [25, 27]. Moreover, with the recent development of Deep rTMS H-coils by Dr Zangen (a consultant on this protocol), it has become feasible to perform rTMS on deeper brain structures such as the insula [28-30].

Insula as a target structure: Several lines of research implicate the insula as a critical substrate in nicotine dependence following evidence that insular lesions produce a loss of self-reported cravings for cigarettes and immediate cessation of smoking without relapse [31,32]. As proposed by Naqvi *et al*., the insula plays a role in the recall of the interoceptive effects of drug taking, and through interactions with other brain regions, mediates conscious urges and decision making precipitating relapse [33]. This hypothesis is substantiated by growing preclinical work: results from studies at our own translational addiction research laboratory reveal that temporary insular inactivation in rats leads to reduced nicotine self-administration and seeking after exposure to nicotine-associated cues or a priming dose [34,35]. Neuroimaging studies further evidence significant associations between cue-induced activation of the insula and self-reported craving for a cigarette [36], with greater bilateral insular pre-quit activity also predicting relapse in smokers [37].

Taken collectively, an intervention which directly modulates insular electrical activity such as deep rTMS may be promising treatment for nicotine dependence. Indeed, a recent investigation revealed improved smoking outcomes following high-frequency deep rTMS non-selectively targeting the insula and prefrontal cortex relative to sham. Specifically, smokers reported reduced cigarette consumption and greater and longer lasting abstinence rates after 2 weeks of treatment [38]. However, the effect of stimulation exclusively to the insula remains to be thoroughly explored in humans. The use of the recently developed H-coil will allow us to address this gap. Although the modulation of structures adjacent to the insula cannot be excluded, this will unlikely be a drawback as results in human smokers suggest that extra-insular lesions do not implicate those areas in smoking behaviors [31]. Similarly, pilot studies from our lab evaluating the effect of inactivating brain areas adjacent to the insula found no significant effects (Le Foll *et al*., unpublished observations). We recently also completed a rTMS study with the H-coil in healthy non-dependent individuals, and our data indicate that our approach is safe and tolerable in humans (data not shown). Finally, as some of varenicline's actions involve down-regulation of the functional connectivity between the insula and regions pertinent to nicotine withdrawal in smokers [39], the combination of varenicline and deep rTMS of the insula is a favorable dual treatment approach. These interventions may synergistically work to yield more efficacious and enduring treatment effects.

Research Question
Can deep rTMS to the insula using the insula H-coil improve smoking outcomes in smokers receiving varenicline?

Aims and Hypotheses
Hypotheses:
Primary: Active deep rTMS intervention will improve point prevalence abstinence rates at the end of varenicline treatment (Week 12) as measured by self-report and confirmed with plasma cotinine levels.
Secondary 1: Active deep rTMS intervention will significantly attenuate craving and reduce cigarette consumption and dependence severity.
Secondary 2: Active deep rTMS intervention will significantly improve short-term point prevalence abstinence rates and long-term prolonged and continuous abstinence rates.

Aims:
Primary: To examine the efficacy of bilateral deep repeated transcranial magnetic stimulation (rTMS; 10 Hz) directed to the insular cortex, relative to sham stimulation, on point prevalence smoking abstinence in smokers who are receiving standard varenicline treatment (2 mg/day).
Secondary 1: To examine the effect of bilateral deep rTMS directed to the insular cortex, relative to sham, on other smoking outcomes throughout study duration including self-reported craving, cigarette smoking and dependence severity.
Secondary 2: To examine the effect of bilateral deep rTMS directed to the insular cortex, relative to sham, on abstinence at the end of rTMS treatment (point-prevalence abstinence at Week 4) and at 6-month follow-up (prolonged and continuous abstinence at Week 26).

Study Design
Overview: This study will be a randomized, double-blind, sham-controlled clinical trial. Specifically, fifty nicotine dependent participants expressing a willingness to quit smoking will be randomized into one of two rTMS intervention arms: Sham (n=25) or Active (10 Hz, n=25). All participants will receive an open-label treatment of varenicline (Week 1 to Week 12), and a target quit date (corresponding to the end of Week 2) will be set for each individual. Participants will also receive brief weekly counselling adapted from the Mayo Clinic's 'Smoke Free and Living It' manual. The rTMS interventions will begin at Week 1 for four weeks (5 sessions a week for a total of 20 sessions), and will be performed with an insula-targeting H-coil. Moreover, follow-up visits will be scheduled weekly for the duration of the medication phase and on Week 26. The primary outcome of the proposed study will be plasma cotinine verified (<15 ng/ml) 7-day point prevalence abstinence as measured at the end of Week 12. Other smoking outcomes (craving, consumption patterns, and dependence) will be captured through standardized questionnaires throughout the study duration. Participants will also have plasma cotinine verified measurements of abstinence at the end of rTMS treatment (end of Week 4), and at the follow-up at 6 months (end of Week 26). This trial will be conducted in compliance with the protocol, GCP, and Canadian Food and Drug Regulations Division 5.

Participants: Participants in the proposed study will be nicotine dependent individuals (n=50). We will recruit through various sources: the community, CAMH clinics, word of mouth, and/or through posters/fliers distributed in and around the research centers as well as on the CAMH website. CAMH approved study recruitment ads will be placed primarily around, but not limited to, the downtown Toronto area. Ads may also be placed in various local newspapers, magazines, community venues (e.g., bars) as well as TTC streetcars, buses and subways. Online advertisement services may be employed, in accordance with CAMH guidelines. Ads and fliers will be approved by the REB. Participants may also be recruited from similar protocols approved at CAMH provided they have agreed to being contacted about future studies.

Recruitment for the study may also be initiated by members of the *Circle of Care* who are treating the potential study participant. These individuals will not obtain consent but they may identify potential research participants and obtain verbal permission for a member of the research team to approach and discuss the study with them. Potential participants who provide assent to be contacted by a member of the research team will then be contacted by a member of the research team who will engage them in the informed consent process if they are agreeable to proceed as such.

Additionally, as part of the CLEARR (Clinical Engagement and Research Recruitment) initiative, a delegated Research Coordinator under the supervision of a CLEARR team recruiting clinician and accountable to the Manager of Research Practice will identify potential participants and notify the research team and the client's clinician about the potential eligibility to participate in the study. The clinician will then ask the client for assent to meet with a study team member to discuss details and participation in the study. Only clients who agree to this process will be approached.

The delegated research Coordinator will access personal health information (PHI) in I-CARE in order to determine eligibility of CAMH participants to participate in the research study. No PHI except MRN will be collected for this purpose and this information will be kept in a secure locked location.

The aforementioned recruitment strategies are in line with our aim to enroll a representative sample of smokers. This is in contrast to more traditional smoking cessation clinical trials, wherein the majority of smokers are often excluded, thereby jeopardizing the generalizability of the data [5]. Our exclusion criteria may be regarded as less restrictive for this purpose. Nicotine dependence will be determined via testing/ measurements stated in the "Screening Assessment" section below.

Interventions and Procedures: Potential participants will undergo a telephone pre-screen to determine initial eligibility. Participants may also complete this screening electronically, through REDCap (see REDCap section). They will subsequently be invited to an in-person Screening Assessment to confirm final eligibility to participate.

Screening Assessment and Consent:
Following the review and signing of the Informed Consent Form, the following measures and assessments will be administered at the screening visit:

1) Fagerstrom Test of Nicotine Dependence (FTND). The FTND is a measure of physical dependence severity [40].
2) Diagnostic and Statistical Manual of Mental Disorders (DSM-V/SCID-V). The DSM/SCID-V will be used to diagnose nicotine dependence in participants [41] and/or any other psychiatric issues.
3) Timeline Follow-Back (TLFB). The TLFB is a reliable method used to detail nicotine (smoking), alcohol and caffeine consumption behavior over a specified period of time. Participants are asked to recall key anchoring events to prompt retrospective estimates of cigarette, alcohol or caffeine intake [42].
4) Expired Carbon Monoxide (CO) Measurements. Breath CO measurements provide a reliable indication of recent smoking status among smokers.
5) Smoking Contemplation Ladder. This questionnaire allows for the measure of readiness to quit smoking in individuals. A cutoff score of 7 is commonly used to determine individuals who are motivated to quit [43].
6) Mini Mental State Examination (MMSE). The MMSE is a gross measure of cognitive status in individuals, with a commonly used cutoff of <24 [44]. The test will serve as indication of cognitive competence to provide informed consent.
7) Medical and/or psychiatric assessment by study physician (or delegate).
8) Blood draw for quantification of cotinine, complete blood cell count, routine blood chemistry and/or beta-HCG (serum pregnancy test, for females).
9) SAFTEE: a technique for the systematic assessment of side effects in clinical trials [45].
10) Drug screen (urine or blood)
11) Demographic and contact forms
12) TASS form (TMS Adult Safety Screening Questionnaire)

Total Number of Study Visits:
In addition to the screening assessment, there will be 30 study visits. The first visit (study start day) will correspond to the 1st varenicline dose and the 1st rTMS session. There will be 4 consecutive weeks of rTMS (20 sessions). Weekly follow-up visits will occur for the 12 weeks of the trial and a final visit will occur at week 26. The TLFB, SAFTEE, concomitant medication log and Adverse Event log will be administered/ updated at every visit. CO measurements will also be taken at every visit. Regular pregnancy testing for females will occur throughout the study. Selective questionnaires (described below in Outcome Measures) will also be administered at study sessions. Urine drug testing will be conducted as required. There will be a total of 4 blood draws (including the screening session). Cotinine blood samples will not be analyzed upon collection. The clinical lab will process the samples and the study stuff will pick up the samples and store them in a -20°C freezer. Analysis will be done in batches of 30 or more samples.

Varenicline Treatment:
All participants will receive varenicline pharmacotherapy, beginning at Week 1, for a total duration of 3 months (12 weeks). A target quit date for all participants will be set for Day 15. The varenicline dosage schedule will be that standard for smoking cessation. It will consist of 0.5 mg tablet once a day for the first three days (day 1 – day 3), followed by four days of 0.5 mg BID (i.e. twice a day: AM and PM; day 4-7). The target daily dose of 2 mg (1 mg BID, i.e. twice

a day: AM and PM) will begin on Week 2 (day 8) and extend until the end of treatment. Subjects will be advised to orally consume the tablet with food and water. Notably, we may use 1 mg daily if 2 mg daily is not well tolerated. The study medication will be dispensed weekly by the CAMH pharmacy. Compliance will be assessed through reported missed doses at weekly visits (see *Follow-up Visits* section below).

rTMS:
Participants will be randomized into either sham (n=25) or active (10Hz, n=25) rTMS intervention in a 1:1 ratio. Brainsway will provide the randomization cards and the randomization list, which will then be managed by an independent person outside of the study. The stimulation protocol will begin in Week 1, and will consist of 5 rTMS sessions per week over the course of 4 weeks (20 in total). Importantly, rTMS will be administered 2 weeks preceding and 2 weeks following the targeted quit date (Day 15), as smokers are believed to be most susceptible to relapse early in the abstinence phase [46]. Both active and sham stimulations will be administered using the insula H-Coil (Brainsway, Model 102B; Jerusalem, Israel), developed by Dr. Abraham Zangen (consultant on this proposal). First, resting motor threshold (RMT) will be determined based on the minimum intensity to cause one of the right hand muscles to activate in at least 5 of 10 trials. The active simulation will comprise of 34 trains of 3 seconds each at 10 Hz and 30 pulses per train and an inter-train interval of 26 seconds. Stimulation intensity will be administered at a target of 120% RMT. Titration of stimulus intensity may occur over the first 4 sessions to enhance tolerability. For participants with poor tolerability the stimulation target will be a minimum of 110% RMT. For the sham stimulation, we will use the same coil placement as that used for active stimulation, matching the number of pulses delivered. The sham coil, which is built into the same helmet, mimics the active coil with respect to acoustics and scalp sensation. Notably, this coil, which allows for the bilateral stimulation of the insular cortex, is presently located at CAMH, and has been used by our team in a recently completed pilot study in healthy controls. Since rTMS sessions will occur daily for 4 weeks, medical staff will be onsite during all procedures and standard procedures for treating patients with rTMS in the Temerty Centre will followed.

Follow-up Visits:
The follow-up visits scheduled on a weekly basis for the duration of the medication phase (Week 1 through to Week 12) will serve a number of purposes. First, as counselling is clinically recommended to be administered alongside smoking cessation medication for increased efficacy [47], a trained study member will deliver brief counselling interventions. The counselling sessions will be adapted from the Mayo Clinic 'Smoke Free and Living It', a commonly used manual in pharmacotherapy trials for nicotine dependence, and will cover various topics aimed at building problem-solving skills and providing support through quitting and withdrawal [48]. Counselling will be provided weekly for the 12 weeks. Second, adverse events will be recorded, and medication compliance will be monitored at follow-up visits. Third, questionnaires will be administered to assess the secondary outcome measures and suicidality of this study (details below).

Clinical study staff may access I-CARE for research record updating as this is a treatment study.

Summary of Events:
Below is a table outlining the assessments, measures, and treatments done at each visit.

		Week and Visit Number													
			W1		W2		W3		W4		W5	W 6-8	W 9	W 10-12	W 13	W 26
		1*	2	3 to 6	7	8 to 11	12	13 to 16	17	18 to 21	22	23 to 25	26	27 to 29	30	31
Assessments & Measures	ICF and ICF quiz	X														
	Contact & Demographic Form	X														
	Medical assessment, SCID, and ECG	X														
	TASS	X														
	MMSE	X														
	Smoking Contemplation Ladder	X														
	Blood draw	X									X				X	X
	CO Measurement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	TLFB (Cigarettes, alcohol, caffeine)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Concomitant Medication Log	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	AE Log	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	SAFTEE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Urine Drug Test	X	X		X		X		X		X	X	X	X	X	
	Pregnancy Test (if required)	X	X		X		X		X		X	X	X	X	X	
	FTND	X	X		X		X		X		X		X		X	X
	Counselling		X		X		X		X		X	X	X	X	X	
	C-SSRS		X		X		X		X		X	X	X	X	X	X
	T-QSU		X		X		X		X		X		X		X	X
	MNSW		X		X		X		X		X		X		X	X
	Point Prevalence Abstinence										X				X	
	Prolonged Abstinence															X
	Continuous Abstinence															X
	RMT for TMS		X													
Treatment	TMS		X	X	X	X	X	X	X	X						
	Varenicline		X	X	X	X	X	X	X	X	X	X	X	X		

*Visit 1 is the screening/baseline visit.

During the TMS treatment (i.e., sessions 2-21) urine drug testing, pregnancy testing, counselling,

FTND, Columbia Suicide Severity Rating Scale (C-SSRS), T-QSU, and MNSW will be done once a week. In the event that a participant misses a session during this time where these assessments were intended to occur, they will be conducted at the following visit. Participants are intended to receive 20 TMS sessions, however, any missed TMS sessions (whether due to the participant or to holiday closure of the Temerty centre) will not be rescheduled.

During the follow up visits (i.e., sessions 22-31), in the event a subject misses a session; they will be able to reschedule the session within the same week. If they are not able to attend within the same scheduled week, the session will be considered as a missed session. The following visits will proceed as scheduled.

COVID-19:
All participants will be screened for COVID-19 symptoms and COVID-19 contacts. If a participant screens positive, they will not continue treatment at that time and the case will be reviewed with Infection Prevention and Control Canada (IPAC) around if, and when, treatment can resume. IPAC recommendations include that all patients and staff wear surgical masks while at CAMH (including waiting areas).

Subject Eligibility Criteria
Inclusion criteria:
1) Age 18-65;
2) Nicotine dependent as assessed by DSM-V;
3) Reported daily cigarette consumption ≥ 10 and expired carbon monoxide (CO) measurement of ≥ 10 ppm;
4) Fagerstrom Test of Nicotine Dependence (FTND) ≥ 4;
5) Reported motivation to quit within 30 days as assessed using the Contemplation Ladder score of ≥ 7.

Exclusion criteria:
1) Reported smoking abstinence in the 3 months preceding screening visit;
2) Current use of other smoking cessation aids;
3) Allergy and/or contraindication to varenicline or rTMS;
4) Pregnancy, trying to become pregnant or breastfeeding;
5) Current or recent history of cardiovascular or cerebrovascular disease and/or current hypertension;
6) Current or historical evidence of suicidal behavior;
7) Serious current or personal history of medical condition/disease (neurological disorders, brain lesions, multiple sclerosis, head trauma, loss of consciousness, hearing loss, etc.);
8) Current, personal history or family history of seizures;
9) Cognitive impairment as defined as a Mini Mental State Examination (MMSE) score <24;
10) Concomitant use of medication that lowers seizure threshold.

Consent
All subjects will provide written informed consent prior to study enrolment. i.e. before undergoing any study-related procedures.

Sample Size and Power Calculation
Based on the results of a recently completed multi-centre trial [4] and results from our previous trial investigating varenicline's efficacy in patients in a residential drug program, we anticipate a 12 week abstinence point prevalence rate of approximately 40% following treatment with varenicline. To detect a clinically relevant 30% difference in the proportion of abstinence between active deep rTMS and sham rTMS treatments with a power of 0.80 ($\alpha = 0.05$), we would need n=42 participants per study arm. However, in light of the pilot nature of this proposed study and the allotted time frame for study completion, we will recruit n=25 participants per study arm (power = 0.66). However, we anticipate attrition with this study sample and as such, we will recruit n=30 per arm to obtain 50 completers in total.

Data Analysis
Descriptive statistics will be used to compare groups (Sham, rTMS) at baseline on main clinical and demographic variables. Fisher's Exact and Mann-Whitney U test will be used for categorical and continuous variables, respectively. Subjects with missing values in the primary outcome (abstinence at 4, 12 or 26 weeks) will be compared with completers on baseline characteristics, to help in the understanding of the reasons for missing values, if at least 10 subjects (20%) are found to be missing. Mixed effect logistic regression that using abstinence at 4, 12 and 26 weeks as dependent variables will be adjusted to the data, with groups and categorical time (4, 12 and 26 weeks) specified as fixed effect, and subject intercepts as random effects. Baseline variables correlated with missingness and/or known to be associated with the outcome will be added as covariates with focus on model parsimony (not to include many covariates) due to small sample size. The primary hypothesis will be tested using a contrast that compares abstinence at week 12 in the logit scale. Similarly, abstinence will also be compared at weeks 4 and 26 as part of our secondary objectives. Mixed effect models that uses maximum likelihood estimation accounts for missingness in the dependent variable by using all available information in the estimation, under the MAR assumption (Missing At Random – the values of a data points are not associated with the missing status of the data point after accounting for relevant covariates) [49]. Other measures related to our secondary objectives (e.g., FTND, CO, TLFB, etc.) will also be analyzed using linear mixed or generalized mixed models, depending on the nature of the outcome of interest. Graphs will be used to explore the data, the models assumptions (for example, residual plots), as well as model results (for example, estimated means plot). Due to small sample, effect sizes with 95% confidence intervals as well as standardized effect sizes will be reported.

Outcome Measures
Main Outcome Measure: 7-day point prevalence abstinence at the end of 12 weeks. This outcome will be measured by self-report of abstinence for the past 7 days, and confirmed using a plasma cotinine measurement of $\leq$15 ng/ml

Secondary Outcome Measures:
1) Fagerstrom Test of Nicotine Dependence (FTND). The FTND will be used to assess physical

dependence severity in participants [40].
2) Expired Carbon Monoxide (CO) Measurements. Expired CO measurements will be regularly taken as a biological confirmation of recent smoking.
3) Cigarettes per day. The Timeline Follow-Back (TLFB) will be used to determine daily self-reported cigarette consumption [42].
4) Minnesota Nicotine Withdrawal Scale (MNWS). The MNWS will be used to assess tobacco withdrawal symptoms [50].
5) Tiffany Questionnaire of Smoking Urges (T-QSU). The T-QSU will be used to assess symptoms of craving/urges for tobacco [51].
6) Point prevalence abstinence at end of 4 weeks: This outcome will be measured by self-report of abstinence for the past 7 days and confirmed using a plasma cotinine measurement of <15 ng/ml.
7) Prolonged abstinence from end of treatment (Week 12) to end of follow up (Week 26). This outcome will be measured by self-report of continuous abstinence since the last visit (at Week 12) and confirmed using a plasma measurement of <15 ng/ml.
8) Prolonged abstinence with 2-week grace period at end of follow up (Week 26). This outcome will be measured by self-report of continuous abstinence since Week 4 and confirmed using a plasma measurement of <15 ng/ml.
9) Continuous abstinence at 6 months: This outcome will be measured by self-report of continuous abstinence since the target quit day (Week 2) and confirmed using a plasma measurement of <15 ng/ml.

The FTND, T-QSU and MNWS will be administered weekly for the first month (i.e. 4 weeks) and subsequently at 8, 12 and 26 weeks.

In the case that a participant declines blood draws, urine will be collected instead for the quantification of cotinine levels.

Study Monitoring and Access to Study Documents
The PI/ QI will permit trial-related monitoring, audits, REB review, and/or regulatory inspections, by providing direct access to source data/documents. This will be mentioned in the Informed Consent Form. Monitoring will be conducted according to the study monitoring plan.

Ethical Considerations
This study is approved by CAMH REB.

Risks and Inconveniences
Blood Collection: Blood collection may cause some bruising and discomfort at the site of needle stick, and rarely, a small infection at the skin puncture site. These risks are minimized by using proper techniques.

Varenicline: Current prescribing practice recommends varenicline be administered at 0.5mg once daily for 3 days, 0.5mg twice daily for 4-7 days followed by 1mg twice daily for the remainder of treatment. According to the varenicline product monograph, the most common side effect of varenicline is nausea, which is dependant on dose. Approximately 30% of subjects treated with 1mg varenicline reported nausea while 16% of subjects reported these symptoms at a 0.5mg

dose. However, this symptom was typically described as being mild to moderate in severity and transient causing only 3% of subjects to discontinued treatment prematurely because of this adverse effect. Other common adverse effects associated with varenicline treatment include sleep disturbances, constipation, and vomiting. There are reassuring data concerning the mental health side effects of varenicline [4]. However, we will monitor suicidality by the Columbia-Suicide Severity Rating Scale. Should any subject begin experiencing significant changes in their mood or behavior, we will ask them to discontinue the medication and contact the study physician or if they cannot contact the study physician, to attend their local emergency room for treatment.

rTMS: When the stimulation is applied to the head, the machine yields a sound. To minimize any inconvenience, ear plugs will be offered to subjects to mute the sound. At certain positions on the head, the stimulation may cause eyes to blink or a brief contraction of the scalp, neck, trunk or upper arm muscles. While these contractions may be annoying, they should not be painful. Some people may experience a mild headache or shoulder stiffness after testing but these symptoms will usually go away in 24 hours. Typically, 1-2 doses (325 mg) of acetaminophen (i.e. "Tylenol") should help to rid these symptoms.

Very rarely, rTMS has been reported to cause seizures. For example, there have approximately been a total of 10 reported seizures when safety guidelines are followed out of thousands of treated patients. However, patients with epilepsy and/or patients with stroke may be more vulnerable to potential seizures. Safety guidelines that minimize seizure risk will be followed. We intend to follow these guidelines and control stimulation so it is well below the maximum limits of the safety guidelines. To our knowledge, no seizures have been reported when stimulation is kept within these safety guidelines. Magnetic brain stimulation (rTMS) has been used on thousands of individuals in the United States, Canada and Europe over several years without any serious problems. That said, the study investigator (or delegate) will be available during rTMS sessions, and will immediately assess and treat any emerging side effects.

Questionnaires: There are no risks associated with the questionnaires, except possibly fatigue. Breaks will be provided as required.

Benefit to participants: Should the dual treatment approach for nicotine dependence be successful, subjects will directly benefit from participation in the study.

Study Documentation

Investigators will retain a participant identification code list if they need to contact participants after the study. This list will contain the complete name, identification number, address, phone number and email of all participants and will be held confidentially at the investigator's site after completion of the study.

REDCap

REDCap will be used as an electronic data capture tool for some questionnaires. If used for this purpose, data collected in REDCap will be considered as source.

REDCap may also be used as a survey for recruitment purposes. For recruitment, the survey will be a stand alone site where participants will answer preliminary questions to determine eligibility. To gain access to the survey, participants will respond to our advertisement by email or telephone. Staff will reply to them with a unique Study ID that the participant will use to gain access to the survey. No PHI will be stored in the same Project as the Survey. At the end of the survey participants will give consent to be contacted and they will be directed to a stand-alone Project with their telephone number and name. The only link between the Survey and Telephone number Project will be a unique Screening ID.

Archiving of Study Documentation
Study data and other essential documents will be retained in a secure setting by the investigators for a period of 15 years as required by current regulations.

Confidentiality
All personal study participant data collected and processed for the purposes of this study will be managed by the investigators and their research staff with adequate precautions to ensure the confidentiality of this data, and in accordance with applicable national and local laws and regulations on personal data protection. The Ethics Committees approving this research, monitors and Health Canada will be granted direct access to all source documents for verification of clinical trial procedures and/or data, without violating the confidentiality of the participants, to the extent permitted by the law and regulations. In any presentation of study results (at meetings or in publications), participant identity will remain confidential.

Participant Safety and Adverse Events
The occurrence of adverse events resulting from varenicline treatment and/or rTMS intervention is a possibility, particularly as we are not excluding various co-morbid disorders. However, in a previous trial completed by our team, we demonstrated the safe use of varenicline in smokers presenting with co-morbid alcohol dependence. Similarly, large recent meta-analyses also reveal the safety of varenicline in smokers with various psychiatric diagnoses [41]. Regardless, possible side effects will be monitored on a regular basis (weekly) during the medication phase. Moreover, we will follow current guidelines for the safe use of both varenicline and deep rTMS, including the exclusion of individuals with any known absolute contraindications to either of these treatments.

The Qualified Investigator (QI) will ensure patient safety. Potential safety concerns and associated solutions will be discussed at regular study meetings. Since this study involves both a pharmacological (varenicline) and device (rTMS with H-coil) intervention, the QI (along with any medical professionals delegated by the QI) will monitor, treat and follow-up on any emerging side/adverse effects. In the event of AEs, the QI will determine severity of the event along with any causal association to the study interventions.

Additional Safety Procedures:
1. Participants will be provided with the QI contact information with an available pager number for 24-hr contact, in case of any unexpected side effects.
2. If necessary, the participants will be transferred home via taxi.

Adverse Events Reporting
Every adverse event and observed device deficiency will be recorded. AEs will be assessed at each study visit. Study staff will question the subject directly asking: how they are feeling and how have they been feeling since last visit. All AEs, whether reported by the subject or observed by study staff/investigators, will be recorded on the AE log along with a brief description, start date/resolution date and any action taken. Symptoms related to smoking cessation will not be recorded as AEs. The AE log will be initialed by the QI, who will make the determination on relationship of the AE to the investigational device/study procedures.

Serious adverse events and device deficiencies meeting Health Canada's mandatory problem reporting requirements (Part 3, Medical Devices for Investigational Testing Involving Human Subjects) will be reported to Health Canada within the reporting time periods required by Health Canada and/or to REB in accordance with REB's local reporting requirements and timelines.

Termination of the Study
Reasons for withdrawing individual subjects from the study may include one or more of the following:

1) Failure to continue to meet inclusion criteria;
2) Severe rTMS side effects;
3) Major protocol violation;
4) Subject lost to follow-up;
5) Withdrawal of consent;
6) Pregnancy
7) The subject missed more than 3 days of TMS treatment during the treatment trial period (not including holiday closures or due to COVID)

Notably, any subject may be discontinued from the study at the discretion of the Qualified Investigator if it is deemed to be in the best interest of the subject.

When participants are prematurely withdrawn they will be replaced by a new participant until the total recruitment aims are met or until the trial is stopped. Replacement will be according to the inclusion and exclusion criteria above and will follow the same procedure as for the original participants. Data collected until the time of withdrawal may be used in analyses.

Criteria for the Termination of the Trial
The study will be terminated upon completion of the recruitment targets. The study may also be terminated due to adverse events or at the discretion of the QI/Sponsor.

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Participant Compensation
Assessment visit: $20
rTMS visits (20 total): $400 ($20/ visit)
9 follow-up visit: $15 per visit (total=$135)

Final follow-up visit: $30
TOTAL: $585
(Taxi vouchers will be provided, if needed).

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