DEPRESSED MOOD IMPROVEMENT THROUGH NICOTINE DOSING 2
(THE DEPRESSED MIND STUDY 2)

PHASE 1: R61 PHASE

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1.0 BACKGROUND

Late-life depression (LLD) is characterized both by affective symptoms and broad cognitive deficits. The co-occurrence of cognitive deficits in LLD, particularly executive dysfunction, is a clinically relevant phenotype characterized by significant disability and poor antidepressant response. Cognitive deficits can persist even with successful antidepressant treatment and increase the risk of depression relapse. Despite the clinical importance of cognitive deficits in LLD, there are no established treatments that specifically target cognition in this population. This is particularly important, as the cognitive deficits appear to directly contribute to disability and poor antidepressant treatment outcomes. **The lack of clear pharmacologic targets and therapies aimed at improving cognitive deficits in depression is a substantial deficiency in current therapeutics**.

We propose that modulation of the cognitive control network by stimulation of cholinergic system nicotinic acetylcholine receptors will improve both mood and cognition in depressed elders. As observed in smokers, nicotine's effect to increase cognitive control network activity while reducing default mode network activity will reduce depression's characteristic bias to negatively valenced stimuli and decrease rumination. Supporting this theory, nicotinic receptor activity stimulates serotonin release and protects against worsening mood with tryptophan depletion. Clinically, transdermal nicotine improves mood in smokers while a placebo-controlled pilot trial in nonsmoking depressed adults found that transdermal nicotine significantly improved mood.

In our initial pilot trial in LLD (1), we demonstrated that open-label administration of transdermal nicotine patches safely improved depression severity. We also observed trends suggesting that transdermal nicotine (TDN) may provide benefit for cognitive performance, specifically in domains of episodic memory, working memory, and attention. In unpublished functional MRI pilot data acquired during this trial, we observed that TDN also enhanced activity in the cognitive control network and that such changes were associated with greater reductions in depression severity.

These data supported a successful application to NIMH for a **R61/R33 proposal**. This grant mechanism initially supports the R61 phase, a 2-year study to establish target engagement of an investigational intervention. If a priori thresholds demonstrating target engagement are met, this would be followed by a 3-year R33 phase. The current protocol only covers the initial R61 study phase.

2.0 RATIONALE AND SPECIFIC AIMS

Cognitive control is a set of interrelated executive processes (2) involving the anterior cingulate-insular salience network and the frontoparietal network. Jointly, these networks are conceptualized as a superordinate "multiple-demand" cognitive control network (CCN) (3,4), involved in emotional regulation, attention, working memory, and inhibiting irrelevant information. CCN dysfunction is a core feature of late-life depression (LLD), contributing to mood disturbances, executive function deficits in inhibitory control and working memory, poor antidepressant responses and disability. Improvement of CCN dysfunction could benefit cognitive performance and mood, but no current pharmacotherapy targets CCN function in LLD.

We propose that enhancement of CCN function by nicotinic acetylcholine receptor agonists (5) will improve mood and cognitive symptoms in LLD (6). This is supported by our **pilot trial** in LLD (N=15) where 12-weeks of open-label transdermal nicotine (TDN) patches significantly improved depression severity (1). In unpublished pilot data using an emotional Stroop task, TDN reduces the difference in fMRI activation between Stroop conditions in a key CCN hub region, the left middle and superior frontal gyri (M/SFG). As TDN also improves emotional Stroop task accuracy and reaction time to incongruent stimuli, in context of past work (5) we propose TDN ***enhances cognitive control function*** (7,8). The M/SFG is a compelling imaging target as the dorsolateral PFC (including the M/SFG) exhibits reduced activation and functional connectivity in LLD (9-13), while antidepressant treatment enhances activity in this region (14,15). Critically, in our pilot data, when TDN administration reduces the difference in M/SFG activation between Stroop conditions, we observe a corresponding reduction in depression severity. Based on these data, ***we hypothesize that nicotinic receptor agonists enhance CCN function in LLD. This effect in the M/SFG, a region exhibiting dysfunction in LLD, benefits depressive symptoms and cognitive performance*** (5,6).

The R61 phase (N=36) will test for target engagement, defined as a TDN exposure-dependent effect on cognitive control network (CCN) activation. Based on pilot data, we will test for enhancement of CCN function by examining the M/SFG Stroop BOLD fMRI response, or the reduction in the M/SFG activation difference between incongruent and congruent conditions of the emotional Stroop task during fMRI. We will assess the effects of variability in nicotine exposure on target engagement by measuring nicotine blood levels in conjunction with repeat MRI.

AIM 1: R61 Phase: Test CCN engagement over 12 weeks of open-label transdermal nicotine (TDN)

Hyp 1A *(Target Engagement)*: TDN will enhance CCN function, measured as a reduction in the M/SFG Stroop BOLD response (the activation difference between incongruent and congruent conditions of the emotional Stroop task). 60% or more of subjects will exhibit a M/SFG z-score reduction of 0.5 or greater.

Hyp 1B (*Exposure*): Higher nicotine exposure measured by patch dose or nicotine metabolite levels will be associated with a greater reduction in the M/SFG Stroop BOLD response.

3.0 ANIMAL STUDIES AND PREVIOUS HUMAN STUDIES

3.a. Overview: Late Life Depression (LLD) has a prevalence of 5% in community-dwelling older adults, high healthcare costs, and a high risk of suicide.(16,17) Individuals with LLD often exhibit a poor response to current antidepressant medications(18) with no differences in response rates between current drug classes.(19,20) Cognitive deficits are common in LLD and associated with disability (17,21-25) and poor treatment outcomes.(26-34) There are no pharmacological treatments targeting cognition in older adults with depression. Drugs developed for AD either have no benefit (35) or may worsen depression.(36)

3.b. Brief Introduction to the Cognitive Control Network (CCN): Cognitive control refers to the ability to dynamically respond to changing contingencies to meet environmental demands.(2,4) Cognitive control mediates executive functions of set shifting and flexibility, inhibition, sustained attention, and working memory.(2,4) These functions are achieved through the cognitive control network (CCN), a regulatory superordinate network consisting of regions more active during executive tasks.(4) The CCN includes regions of frontoparietal cortices with network hubs in the dorsolateral prefrontal cortex (dlPFC), posterior parietal cortex and the dorsal anterior cingulate cortex (dACC).(4) Recent CCN models include salience network regions (37,38) conceptualizing the CCN as a “multiple demand” network addressing diverse cognitive challenges.(39)

3.c. Cognitive control deficits in LLD: CCN deficits in LLD clinically manifest as executive dysfunction in selective attention, working memory, response inhibition, and performance monitoring. CCN-mediated executive dysfunction is common in LLD,(40-43) clinically presenting as difficulty with planning, sequencing, organizing, and abstracting. Although also influenced by processing speed,(44) CCN dysfunction negatively affects other cognitive domains including verbal learning and recall.(45,46) CCN dysfunction predicts negative clinical outcomes, including poor acute responses to antidepressant medications.(28,32,34,47) CCN-mediated cognitive performance deficits may persist into remission (48-51) and are associated with persistent disability.(52) Antidepressant treatment enhances activity in this region while therapeutic benefit may arise by targeting this region. (14,15,53-55) Much of this work focuses on the dlPFC, a CCN region including the middle and superior frontal gyri (M/SFG).(56,57)

CCN dysfunction also contributes to emotion dysregulation.(58) The CCN is involved in explicit emotion regulation,(59) automatic and effortful processes that modulate emotional responses.(59) For example, difficulty inhibiting ruminative or negatively valenced thoughts may lead to persistent depressive symptoms.(46)

3.d. Nicotine effects on depressive symptoms: The concept that there is an association between cholinergic function and depression dates back decades. The original cholinergic hypothesis of depression by Janowsky and colleagues proposed that depression is associated with hyperactivation of the cholinergic system, resulting in decreased noradrenergic activity (60). Pharmacologically, cholinergic effects on mood must be mediated either by the nicotinic receptor (nAChR) family or the muscarinic receptor (mAChR) family. The cholinergic

hypothesis is supported by observations that smoking rates are high in MDD (61,62) while depressed smokers have difficulty with smoking cessation and are at risk for depression relapse during smoking cessation (63-68). However, these data do not inform about specific effects of nAChR stimulation.

Animal models support that modulation of nAChR activity may be beneficial in depression (69,70). Several studies in rat models of depression demonstrate that nicotine and nAChR agonists reduce depressive behavior (71-77). Clinical studies in humans support that nAChR stimulation may have antidepressant properties. The few studies examining nonsmokers with MDD **demonstrate that transdermal nicotine administration results in significant improvement in mood** (78-80) and may have long-term efficacy comparable to that of fluoxetine (81). Although these studies examined small samples, nicotine exhibited antidepressant effects even at low doses in a placebo-controlled trial (79). To our knowledge, **only our pilot 12-week trial has examined individuals with LLD.** Our study supports that transdermal nicotine may have clinical benefit for depressive symptoms (Fig 1).(1)

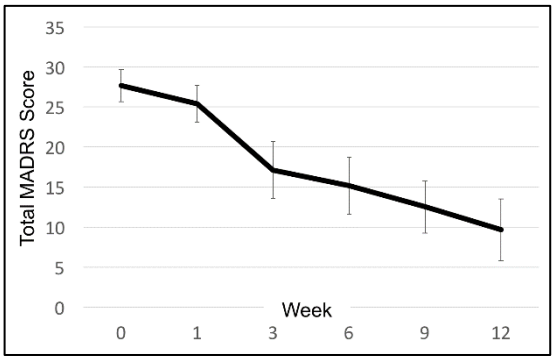


Figure 1 Transdermal nicotine effects on depression severity over time

3.e. Nicotine as a cognitive enhancer: The cholinergic system is the primary neurotransmitter system responsible for cognitive symptoms in dementia (82), with nicotinic receptors being particularly important (83). Neuronal nicotinic receptors (nAChRs) are found throughout the central nervous system and nicotinic innervation of the hippocampus, amygdala and frontal cortex are vital to memory function (Levin 2000)(84). In addition to direct stimulation of nAChRs, nicotine stimulates the release of a variety of transmitters involved in cognitive function, including dopamine, norepinephrine, serotonin, and glutamate (85,86).

Cognitive improvement is a well-established effect of nicotine. A recent meta-analysis of over 41 double-blind placebo-controlled studies concluded that nicotine has positive effects on attention, memory, and motor abilities which likely represent true performance enhancement (87). In smokers, nicotine improves performance on attentionally and cognitively demanding vigilance tasks (88-90) even in the absence of withdrawal effects (87,91). The nicotinic system appears to modulate controlled attentional processing when task conditions are difficult (92-94). Past work in impaired populations further supports that nicotine improves CCN-mediated cognitive domains including working memory, learning and attention.(6,87) Specifically, nicotine may show particular benefit for cognitively demanding tasks requiring focused attention despite distracting stimuli.(95,96) Nicotine also benefits episodic memory [87] although this may be mediated through improvements in attentional functioning.(95)

3.e.1. Clinical Studies of Nicotinic Stimulation for Cognition in Olde Populations*:* Newhouse and colleagues first showed evidence of impro memory with intravenous nicotine injection in Alzheimer Disease (AD) subjects (97). Subcutaneous nicotine injection (98,99) and nicotine skin patch treatment also significantly improves cognitive function in AD patie (100,101). In AD, nicotine improves attention and lessen errors (102). Newhouse extended this work to show that the novel nicotinic agonist A 418 also has positive effects on learning and memory in AD (103). More recently, **Newhouse and colleagues (104) showed that chronic transdermal nicotine treatment improved attention and episodic memory in patients with Mild Cognitive Impairment (MCI) (**see Fig 1 and 2**).** These findings are being examined in a NIA-funded multi-site MI Study (Memory Improvement through Nicotine Dosing; Newhouse, PI).

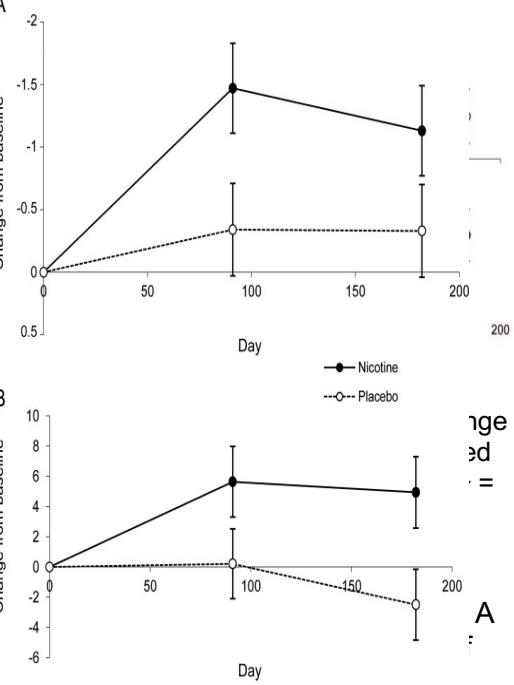


Figure 2. Episodic Memory.
A) Paragraph recall, nicotine > placebo ($F_{1,60}$=4.42, p=0.04). B) Word recall, nicotine > placebo ($F_{1,70}$=5.92, p=0.018).

3.f. Pharmacoimaging studies of nicotine: Work in smokers and nonsmokers led to hypotheses (5,95,105) that nAChR agonists benefit c information processing while decreasing activity in regions involved in ta meta-analysis examining task-independent effects of nAChR agonists su

activity changes.(5) First, nAChR agonists enhanced activation in CCN regions, including the dorsal ACC, lateral prefrontal and dorsomedial prefrontal cortices. Second, nAChR agonists decreased activation in other regions, reflecting enhanced deactivation in the ventromedial prefrontal cortex, posterior cingulate cortex, and parietal cortex. Thus nAChR agonists have general neuropharmacological effects of enhancing activation in CCN regions while decreasing activation in default mode network (DMN) regions.(5)

3.g. Safety of transdermal nicotine (TDN) patches: TDN patches are well tolerated, with a meta-analysis in over 5500 individuals(106) identifying only minor adverse effects such as sleep disturbances, nausea, and minor skin irritation. Few adverse cardiovascular events were reported, with no excess of events occurring among patch users compared to placebo. This is concordant with our prior 6-month trial in Mild Cognitive Impairment(104) and our pilot LLD trial.(1) We have not observed withdrawal or craving in past studies.

In our LLD Pilot trial, participants exhibited > 95% compliance with study patches. There were no SAEs and the most common adverse effects included nausea (N=7), dizziness (N=4) and headache (N=4). These were dose-limiting in 7 subjects (including 1 early withdrawal). We observed no significant changes in blood pressure or heart rate but observed a decrease in weight (6.7lb, t= 4.30, p<0.01). Individuals who received TDN with an antidepressant tolerated a higher mean dose than those receiving TDN monotherapy (p<0.01). We observed no ill effects or craving after tapering and discontinuing TDN over an additional 3 weeks.

4.0 INCLUSION/EXCLUSION CRITERIA

Men and women of all backgrounds are eligible. Criteria are similar for both phases.

Inclusion Criteria:
1) Age ≥ 60 years;
2) diagnosis of major depressive disorder, single or recurrent episode (DSM5);
3) On a stable therapeutic dose of an allowed SSRI or SNRI for at least 6 weeks;
4) severity: MADRS(107) ≥ 15;
5) cognition: MMSE(108) ≥24;
6) fluent in English

Exclusion Criteria:
1) Other Axis I psychiatric disorders, except for generalized anxiety disorder (GAD) or social phobia symptoms occurring in a depressive episode;
2) Use of other medications for depression, e.g., bupropion or augmenting agents, although short-acting sedatives are allowed (see below);
3) Any use of tobacco or nicotine in the last year;
4) Living with a smoker or regular exposure to secondhand smoke;
5) History of ~~alcohol or drug dependence or abuse in the last 3 year~~ alcohol use disorder or substance use disorder of moderate or greater severity (endorsing 4 or more of the 12 criteria) in the last 12 months;
6) Acute suicidality;
7) Acute grief (<1 month);
8) Current or past psychosis;
9) Primary neurological disorder, including dementia, stroke, epilepsy, etc.;
10) MRI contraindication;
11) Electroconvulsive therapy or transcranial magnetic stimulation in last 2 months;
12) Current or planned psychotherapy;
13) Allergy or hypersensitivity to nicotine patches;
14) In the last 4 weeks, regular use of drugs with central cholinergic or anticholinergic properties or moderate / severe CYP2A6 inhibitors /inducers (**see Appendix B)**

Allowed Antidepressants: Eligibility criteria require current use of a commercially available antidepressant medication at a therapeutic dose. To decrease variability in the underlying antidepressant regimen, we define a therapeutic dose of allowable antidepressants as: fluoxetine(20mg), sertraline (50mg), citalopram (20mg), escitalopram (10mg), venlafaxine (75mg), desvenlafaxine (50mg), levomilnacipran (40mg) or vilazodone

(20mg), duloxetine (30mg) or their equivalents. Higher doses are allowable.

Due to anticholinergic effects, effects on nicotinic acetylcholine receptors, or other safety concerns, we exclude for and do not allow for the use of some antidepressants. These exclusions include**: a)** paroxetine; b) bupropion; c) tricyclic antidepressants; and d) monoamine oxidase inhibitors. We also exclude for current use of ketamine or esketamine for depression.

Concomitant Medications: Most non-psychotropic medications are permitted. The exceptions are for medications with substantial procholinergic or anticholinergic properties or medications influencing CYP2A6 activity (**see Appendix B**), the main pathway for nicotine metabolism.(109) **Prohibited** cholinergic agents include but are not limited to acetylcholinesterase inhibitors and some agents used for tremor, incontinence, or vertigo. We allow short-acting hypnotics (zolpidem, zalpelon, or eszopiclone) and lorazepam up to 2mg daily for sleep or anxiety.

5.0 **ENROLLMENT AND CONSENT**

5.**a. Recruitment** :We will enroll patients from clinical referrals and response to advertisements. For clinical referrals, referring providers may either provide information about the study to the participant, including our contact information. Alternatively, they may obtain permission from the participant for the study team to contact them. With the clinician's agreement, study staff can review their clinic schedules to help identify potentially eligible patients, however data will not be recorded for research purposes. Advertisements may include radio, newspapers, internet, and flyers / brochures. When responding to advertisements, potential participants will contact us by telephone or through email. During the initial contact, we will describe the study purpose and procedures to them, including a description of study entry criteria. Those who continue to be interested will then be scheduled for an evaluation. After scheduling, a study doctor will review their electronic medical record to assure that potential subjects meet entry criteria, however no data will be recorded. If that review determines the individual is not eligible, they will be informed, the screening visit cancelled, and the referring clinician notified.

In order to enhance the recruitment efforts, this project is using the services of Trialfacts.
Trialfacts is a third-party service which provides specialized recruitment methods in digital advertising. Trialfacts provides marketing strategies and campaigns to speed up participant recruitment by leveraging social media and digital platforms. Trialfacts creates GCP-compliant advertising and recruitment materials used in the recruitment process, including study information pages, landing pages, pre-screening questionnaires, and online advertisements. They will only share IRB approved materials with referrals. Interested candidates will sign a study interest form and be directed to research staff, who will further screen potential participants.

5.b. Enrollment and Consent: Potential participants will be initially evaluated using our current telephone or REDCap screening approach. If they appear eligible, they will be scheduled for an in-person or Zoom screening evaluation. Upon presenting for evaluation, we will obtain formal written consent from all participants. Following policies of the Vanderbilt University Health System Institutional Review Board, written informed consent will be obtained and documented by the study's Research Coordinator before any study-related procedures are performed. The study coordinator will review study procedures and the consent form with each potential participant. A study doctor will be available should any consent-related questions arise. Each individual may take as much time as they like to decide if they do or do not wish to participate.

We also allow that participants can be consented without coming physically to VUMC. This will be conducted via HIPAA compliant Zoom teleconferencing, as is recommended for telemedicine. We will use Facetime or other videoconferencing software it there are any technical difficulties on Zoom or at the participant's request. An e-consent process will be conducted using a REDCap-based electronic consent form. The consent form has been developed in REDCap, a secure, web-based, HIPAA-compliant, data collection platform with a user management system allowing project owners to grant and control varying levels of access to data collection instruments and data (e.g. read only, de-identified-only data views for other users. A study coordinator or

approved study staff will review the consent form while teleconferencing with the participant and answer any questions before the participant signs.

Patient signatures will be obtained using REDCap's 'Signature' field type on the survey. Upon completion of the consent, participants will be able to download a signed copy of the consent form. We will also provide them with a copy of their version of the consent document signed by them and by the consenting study staff member by mailing of a hard copy of the consent.

A deidentified document confirming that each participant has provided signed informed consent will be signed by the research coordinator and the Principal Investigator and kept in the research file.

5.c. Anticipated Enrollment: Accounting for screen failures, we anticipate consenting up to 60 subjects total to have 36 individuals complete baseline procedures and start study patches.

6.0 **STUDY VISITS AND ASSESSMENTS**

Overview: After a screening visit to confirm eligibility and diagnosis, participants will then be scheduled to complete a baseline assessment consisting of a broad symptom assessment, memory testing, and cranial MRI. They will then complete 12 weeks of open-label transdermal nicotine patches. At the end of the 12 weeks, they will then repeat baseline assessments, have blood drawn for measurement of nicotine metabolites, and have study drug tapered over three weeks.

6.a. Assessment Burden: The clinical and cognitive batteries are similar to those used in our past LLD studies. They are not burdensome and we allow breaks. Refer to the separate "Schedule of Events" file for a timing of all procedures.

6.b. Initial Evaluation: In the initial screening evaluation, current and past psychiatric diagnoses are assessed with the **MINI (Mini-International Neuropsychiatric Interview),** followed by a clinical interview with a study clinician that will assess age of initial onset. The study clinician will assess antidepressant exposure in the current episode using a modified Antidepressant Treatment History Form (**ATHF**)(110,111) updated to include current medications approved for MDD. Medical history and comorbidity will be quantified with the Cumulative Illness Rating Scale-Geriatrics (**CIRS-G**).(112) Screening for cognitive impairment occurs with the MMSE, requiring a score of $\geq$ 24.

Concomitant medication use will be documented and anticholinergic burden quantified using the Anticholinergic Cognitive Burden (**ACB**) Scale.(113) We selected this approach as the ACB scale is sensitive to drug effects on cognition and disability, while serum anticholinergic activity is not consistently associated with cognition.(114-116)

Smoking history will be assessed by self-report items from the PhenX toolkit.(117) Questions include duration and amount of past smoking, symptoms of smoking dependence, and secondhand smoke exposure.

Participants will also complete secondary self-report measures of depressive symptoms, including rumination (the Ruminative Response Scale) (118), apathy (Apathy Evaluation Scale, AES) (119), sleep (Insomnia Severity Index, ISI), worry (Penn State Worry Questionnaire, PSWQ), fatigue (Fatigue Severity Scale, FSS), anhedonia (the Dimensional Anhedonia Rating Scale, DARS), anxiety (the Generalized Anxiety Disorder 7 item scale, GAD7; the Anxiety Severity Index 3; ASI3) and participant's social support , including frequency of contacts, subjective and instrument support (Duke Social Support Index, DSSI). They will also complete self-reports of perceived cognitive performance, including both the PROMIS Applied Cognition Abilities Short Form and the Attentional Control Scale. Finally, disability will be measured with the World Health Organization Disability Assessment Schedule (WHODAS) 2.0.

6.c. Study Visit Schedule: After the baseline visit, where MRI, cognitive, and self-report data are acquired, participants will be seen every 3 weeks (+/- 4 working days), allowing us to assess tolerability prior to dose increases. At each study visit (Weeks 0, 3, 6, 9, 12), depression severity will be measured using the MADRS, administered by a study physician. Vital signs (weight, heart rate, blood pressure) will be measured. Blood

(10ml) will be drawn at each visit after baseline (Weeks 3, 6, 9, 12) to measure levels of nicotine and nicotine metabolites.
Side effects are assessed at each visit using the Frequency and Intensity of Side Effects Rating / Global Rating of Side Effect Burden (**FISER/GRSEB**) scales.(120) Adherence will be assessed using a count of empty wrappers, returned unused patches, and monitoring of blood levels. The Quick Inventory of Depressive Symptoms—Self Report questionnaire (QIDS-SR) will provide a self-report measure for depressive symptoms at baseline, weeks 3,6,9 and 12.

Safety and thoughts of suicide will be assessed at every contact. Individuals endorsing thoughts of death will be questioned by a psychiatrist about thoughts of suicide, intention, and potential plans. When there are concerns for safety, subjects will be withdrawn from the study and treated per clinical care.

MRI, cognitive data, and self-report measures (both depressive symptoms and perceived cognitive performance) will be repeated at weeks 6 and 12.

7. COGNITIVE ASSESSMENTS:

7.a. Negativity Bias (Secondary Outcome**):** To evaluate negativity bias, we use an out-of-scanner, adapted version of the *Trait Adjectives Task*.(121) Participants view a series of randomized, rapidly presented positive and negative characteristics and quickly indicate whether each adjective does or does not apply to them. This is followed 15 minutes later with a test of emotional memory ,where in participants must recall the adjectives they have viewed. Positive and negative adjectives are balanced and selected from a normed list, matched for word length and arousal.(122) Measures include number of adjectives endorsed or rejected, and RT for those trials. Task performance assesses self-referential negativity bias and is associated with antidepressant response.(123) This task will be administered at baseline, week 3 ,week 6, week9 and week 12. The follow-up test of emotional memory will only be conducted at baseline and week 12.

7.b. Cognitive Domain Performance (Secondary Outcomes**):** These tasks are administered out -of-scanner at baseline and week 12.

- *Executive Function***:** Executive function will be measured using the NIH EXAMINER computerized test battery (124). The EXAMINER battery assesses multiple domains:
    - *Inhibition***:** Inhibition will be measured using the Flanker task (using arrows and response to stimuli to probe spatial reorientation); the Continuous Performance Test (CPT)(125) (responding to some stimuli and not others); and an antisaccades eye movement task, (where they move their eyes in the same or opposite direction of a stimulus).
    - *Working Memory*: Assessed using the dot counting task and the N-back task. We will use the 1- and 2- back conditions with alternative versions for repeated testing.
    - *Set Shifting*: Participants will match a stimulus on the top of the screen to one of two stimuli on lower corners of the screen.
    - *Fluency*: Tests of phonemic (letter fluency) and category fluency
    - *Planning*: Using the “Unstructured Task”, subjects complete multiple cognitively simple puzzles
    - *Insight*: Participants then rate themselves on their performance compared to 100 individuals of their same age and education.

  The EXAMINER battery’s primary outcome is its Executive Composite score. Secondary outcomes include its factor scores: Cognitive Control, Fluency, and Working Memory. The Executive Composite and Factor scores are calculated from the tasks above.
- *Psychomotor Speed***:** The **Choice Reaction Time** task will be used as a test of psychomotor speed. Participants must hold a button down until a light appears above one of several other buttons, then move to push that button as quickly as possible. This task measures both response and psychomotor speed.
- *Episodic Memory*: We will utilize the complex **Selective Reminding Task** as a test of immediate and delayed verbal memory.(126) This is an 8-trial, 16-word test where the interviewer reads unrelated words to the participant who must recall them. Any missed items are then repeated before the next attempt. Alternative word lists are available for repeated assessments. A delayed trial is administered after 20 minutes.

8. STUDY DRUG ADMINISTRATION:

8.a. R61 Transdermal Nicotine Dosing: Participants will wear the study patch during the day and remove it at night (16 hours). Titration will be **slower** than in our pilot project(1) in order to improve tolerability. Per our revised schedule (**Table 1**), participants will receive patches starting at 3.5mg daily, increasing to a maximum of 21mg. Doses *can be reduced* to the previous level if needed for tolerability. In these cases, if the precipitating adverse event resolves, the participant can be rechallenged once at the higher dose. If the adverse event reemerges, the participant can again be reduced to the prior dose, but cannot be rechallenged again. This protocol has been added to Dr. Newhouse's (co-investigator) IND 131918 for nicotine transdermal patches.

Table 1. TDN Dosing

Week	Days	Patch Strength	Patch Application	Dose
1	MRI			
1	1-7	7mg	0.5	3.5mg
2-3	8-21	7mg	1	7mg
4-6	22-42	21mg	0.5	10.5mg
6	MRI			
7-9	43-63	14mg	1	14mg
10-12	44-84	21mg	1	21mg
12	MRI			
13-14	85-98	14mg	1	14mg
15	99-105	14mg	0.5	7mg

8.b. Assessment Blinding: Study clinicians conducting the MADRS will be blinded to levels of nicotine or nicotine metabolites and results of the functional MRI studies until participants have completed the 12-week trial.

8.c. Design Rationale: We obtain MRI biomarker data at 6- and 12-weeks. This provides an opportunity to examine the relationship between exposure and target engagement at lower and higher doses. Moreover, for individuals who cannot tolerate higher doses, it provides a naturalistic opportunity to examine target engagement across time in individuals on a stable dose. Other designs, such as a single administration dose-finding study, are not feasible given poor tolerability of higher doses without gradual titration.

We obtain nicotine and metabolite levels every 3 weeks. This will support analyses of target engagement and allows us to conduct exploratory analyses of: a) the relationship between dose and exposure in an elderly, nonsmoking population; and b) the relationship between dose, metabolism, and adverse events.

8.d. End of study medication procedures: Following completion of the 12-week trial, doses will be slowly lowered and study drug discontinued over 3 additional weeks (Table 1). This time can be shortened for participants who do not reach the target dose of 21mg daily. If individuals feel the study drug has provided benefit and elect to continue its use by purchasing over-the-counter patches, we will not require this discontinuation. Subjects will return for a final safety assessment. For individuals who have tolerated study patch well, this final safety visit can optionally be conducted by telephone.

9. MRI PROCEDURES

9.a. MRI Screening: To assure safety for MRI, we carefully screen participants for metal. Working with the Vanderbilt University Institute for Imaging Science, we identify past medical procedures and surgeries that may include metal implants. In these cases, we request medical records to determine if metal was used, and if so, if it is safe for 3Tesla MRI. However, in some cases these records cannot be obtained. In such cases we may obtain an x-ray if there was a question whether there was or was not implanted metal.

We will only obtain an x-ray in cases where a) there is a safety concern about a potential implant or metal; b) medical records for the surgery are not available; and c) participants do not think that metal was involved in the surgery. Thus this procedure will not be needed for the majority of participants. If the x-ray shows there is implanted metal that could be a MRI contraindication, that participant will be withdrawn from the study. Radiation exposure will vary dependent on the area needing to be evaluated.

9.b. Image Acquisition: We will image subjects at the Vanderbilt University Institute for Imaging Science (VUIIS) on a 3T research-dedicated MRI using a protocol that acquires multi-contrast data to allow automated tissue identification and BOLD data at rest and during the cognitive task. Cranial MRI will be performed over 1 hour. Similar MRI durations have been well tolerated in our past studies of LLD. This protocol includes T1-

weighted and fluid-attenuated inversion recovery (FLAIR) images. Functional MRI BOLD acquisitions will be obtained at rest where subjects have their eyes open and focus on a fixation cross and during the emotional Stroop task. Subjects will complete the emotional Stroop task twice (13.5min each; 3mm isotropic voxels, TR=2sec). The emotional Stroop task is presented in E-Prime and described below. Prior to MRI, participants practice the task outside the scanner.

9.c. fMRI Tasks:

Participants will complete two fMRI tasks during each scan.

Similar to our pilot study, for this proposal we will use an **emotional Stroop task**.(127) The classic Stroop paradigm was modified and adapted to an emotional conflict task in which faces with fearful and happy expressions are presented with the words "happy" or "fear" written across them. We ask subjects to identify the emotional expression of the faces while ignoring the words, which are either congruent or incongruent with the facial expression. Incongruent stimuli are thus associated with a response conflict that arises from an emotional incompatibility between task-relevant and task-irrelevant stimulus dimensions (e.g., a fearful expression with the word "happy"). This task dissociates neural systems involved in resolving conflict between congruent versus incongruent emotional distractors.(127,128)

Participants will complete two runs of 148 trials for a total of 27 minutes of testing. Behavioral response times and neural activation will be analyzed as a function of target congruency. The main variable of interest will be activation (percent signal change) of the CCN in response to incongruent-congruent stimuli.

Our co-I Dr. Gunning obtained emotional Stroop fMRI data on 10 elders before & after 12 weeks. The intraclass correlation coefficient (ICC) for the MFG was 0.61. This is consistent with the literature on reliability of task-elicited activation in older adults (129) and qualifies as good reliability for repeated assessments.

Participants will also complete a **scene processing task.** While in the scanner, participants will view images of scenes, faces, and scrambled images for a brief (4 minute) run. Images are projected to a mirror above the participant's head from a projector located outside the scanner room. Stimuli will be presented in the center of the screen at a rate of 750 ms, with a 250 ms interstimulus interval. During the instruction phase, the participant views a series of instruction screens while the rater reads the task instructions aloud. Following instructions, participants are asked to practice the task and are allowed to ask questions freely. Participants will complete 1-2 runs of this task. Scenes depict indoor or outdoor locations (e.g., building exteriors or interior rooms). Face images depict male and female faces with neutral or pleasant expressions. To maximize participants' attention to the images, on some trials an image will be repeated. Participants will be instructed to push a button to detect these targets. Runs with performance less than 50% correct will be excluded from final analyses.

9.d. Image Processing: Functional MRI Analysis: fMRI data will be preprocessed and analyzed using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/). Given the longitudinal nature of our analyses, we will use the SPM12 pairwise longitudinal module to create an average MPRAGE image that can be applied to the functional scans. Standard fMRI preprocessing steps will be utilized, including realignment/ motion estimation, slice-timing correction, ART outlier detection, coregistration of functional and averaged anatomical images and normalization to the MNI template, and spatial smoothing. First-level analyses include motion regressors.

Examining CCN Engagement: To assess target engagement, we will use ROI-level data in native space. To generate these data, middle and superior FG will be identified on individual MPRAGE images using the Neuromorphetrics atlas (academic subscription; http://neuromorphometrics.com) implemented in SPM. For each subject, session, and ROI we will calculate the average percent signal change for the primary contrast of incongruent-congruent trials. We will examine the difference in M/SFG activation between Stroop conditions prior to and after TDN administration using a change z-score. This will provide ROI data for the Go Decision.

Testing for DMN Involvement: To assess potential DMN involvement, we will use an identical approach as for the CCN. We will focus on key DMN hub regions,(130-132) the medial PFC and precuneus.

9.e. Resting State Functional Connectivity Analysis: Preprocessing uses the Conn toolbox in SPM 12 with

standard steps of: realignment of the functional runs and correction for head motion, coregistration of functional and anatomical images, segmentation of the anatomical image, normalization of the anatomical and functional images to the standard MNI template, and spatial smoothing with a Gaussian filter. The resulting BOLD time series will be band-pass filtered to further reduce noise and increase sensitivity.

First-level individual whole brain seed-to-voxel functional connectivity maps will be created for each CCN seed (6mm sphere) in the bilateral MFG and SFG as well as DMN seeds in the medial PFC and bilateral precuneus. Second-level ANCOVAs will test for differences between baseline and subsequent acquisitions, controlling for age and sex while adjusting for multiple comparisons using at FDR = 0.05. Beta values (difference between baseline and subsequent acquisitions) for significant clusters will be further examined to determine the strength and direction of change.

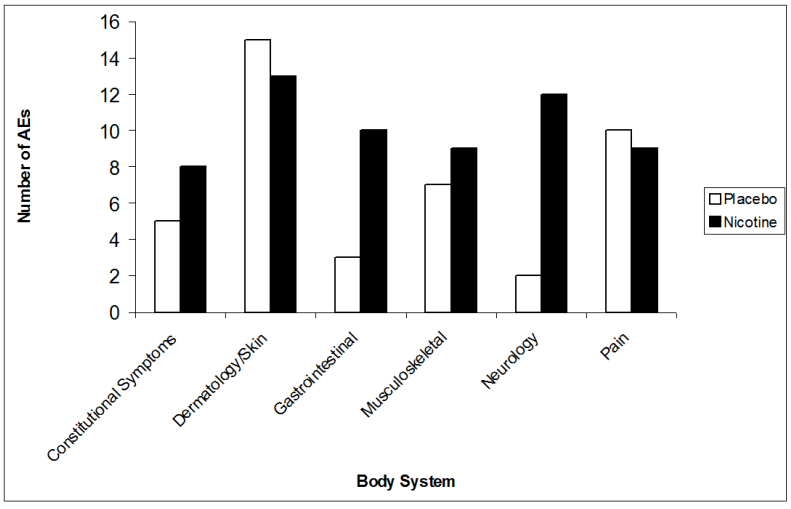
10. MEASUREMENT OF LEVELS OF NICOTINE AND NICOTINE METABOLITES

Every 3 weeks participants will have 10ml of blood drawn to measure metabolites including nicotine, cotinine, and 3 hydroxycotinine. This will occur after at least 2 weeks on a stable dose, and approximately 4 hours after patch application. This schedule allows for participants to be at steady-state levels.(133) These data will provide information on drug level exposure and the nicotine metabolite ratio (3hydroxycotinine / cotinine), a measure highly correlated with the rate of nicotine clearance.(134,135) Samples will be stored at -70 degrees until sent for analyses to Dr. Tyndale at the University of Toronto. These compounds will be quantified by LC-tandem mass spectrometry.(136)

These samples will be de-identified including only the study coded identifier and first and last subject initials. They will also include the date of the blood draw. Permission for sharing of samples with Dr. Tyndale is included in the informed consent document.

11. RISKS – STUDY DRUG

Side Effects of Nicotine: At the nicotine doses proposed in this study, the major peripheral action of nicotine is facilitation of impulses through all autonomic ganglia, stimulation of the adrenal medulla and stimulation of sensory receptors including chemoreceptors in the carotid body. Ganglionic depression occurs at higher nicotine levels. In cardiovascular systems, mild increases in heart rate and blood pressure from sympathetic ganglion stimulation, catecholamine release from adrenal medulla, and aortic and carotid body chemoreceptor stimulation may occur. A mild parasympathetic response may be seen in the gastrointestinal tract and bladder (increased tone and motor activity), with increased secretion of exocrine glands. Nausea and vomiting can occur from peripheral (bowel activity and vagal efferent nerve stimulation) and central (medullary emetic chemoreceptor trigger zone stimulation) causes. Low dose stimulation of the CNS could in theory produce tremors and respiratory stimulation, although this is rarely seen except in patients with tremor disorders. Toxic nicotinic doses result in CNS depression. With use, tolerance develops to virtually all acute adverse effects.



General Safety Experience with the Nicotine Transdermal Patch: A large meta-analysis was conducted examining data from 35 clinical trials utilizing the transdermal nicotine patch in over 5500 individuals (106). Few adverse cardiovascular outcomes were reported and no excess of these outcomes was detected among patients assigned to nicotine patch use compared to placebo patch users. Minor adverse effects such as sleep disturbances, nausea, localized skin irritation, and respiratory symptoms were elevated in patch users compared to placebo users.

In our published MCI trial (104), total adverse events (AEs) for the double-blind treatment period were 82 for nicotine versus 52 for placebo ($p < 0.05$). However, the majority of AEs were mild (nicotine 57.3 %; placebo 54.9%) and there was no statistically significant difference in the proportion of adverse events within the different severity classifications between treatments (Mann-Whitney test $p = 0.97$). No severe AEs were classified as related to drug treatment in either treatment group. Adverse event rates by body systems reported in more than 10% of subjects (Figure) were generally comparable with the exception of gastrointestinal and neurological for which there were more AEs reported in the nicotine-treated group. Approximately 75% of AEs in both placebo and nicotine groups were judged not related or doubtfully related to treatment. More nicotine-treated subjects (N=4) discontinued treatment for adverse events than placebo-treated subjects (N=0) ($X2 (1) = 3.79$; $p = 0.05$). No withdrawal symptoms were reported by subjects or informants nor were any subjects reported to be continuing to use nicotine after the six-month study was completed.

Dermatologic Safety: The most common adverse side effect of the nicotine transdermal patch is skin irritation and accounted for approximately 25 percent of adverse event reports regarding the nicotine transdermal patch to the FDA (137). These effects consist of erythema, pruritus, edema, and rash. Mild skin irritation is common and generally occurs after three weeks of continuous use. Mild to moderate reddening of the skin is seen in 25% of subjects and transient itching in 29%. More severe reactions requiring modification of treatment have been reported in up to 12% of users (DrugDex Drug Evaluation Monograph). Management of the symptoms is usually straightforward and is accomplished by patch rotation, local treatments, and instructing the patient to remove the patch prior to going to bed. Dr. Newhouse has experience in administering transdermal nicotine for over five years to a non-smoking patient with Huntington's disease for movement disorder control. This long-term exposure has been extremely well tolerated with only minor skin irritation seen.

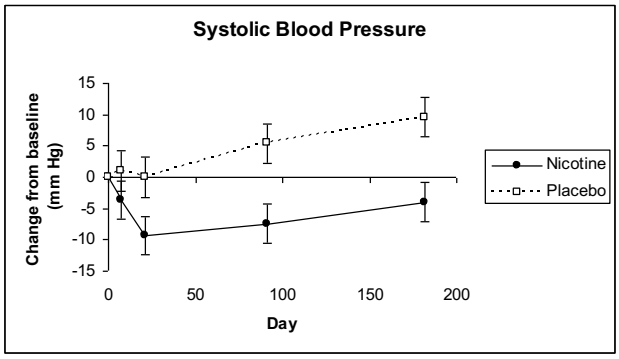
Cardiovascular Safety: There are a number of mechanisms whereby nicotine could potentially cause or aggravate cardiovascular disease (138). Nicotine stimulates CNS sympathetic systems and increases release of catecholamines from the adrenal and vascular nerve endings. While tolerance appears to develop to these cardiac stimulatory effects, the tolerance developed is only partial. While there may be a small chronic cardio-stimulatory effect (approximately seven beats per minute), the dose response curve appears to be flat (138).

However, studies have not demonstrated that nicotine replacement therapies are associated with increased cardiovascular risk or increased incidence of cardiovascular adverse events (DrugDex Drug Evaluation Monograph). The largest and longest such study was the Lung Health Study that enrolled almost 6000 individuals in a study over 5 years involving nicotine replacement therapies for smoking cessation. In this group with chronic lung disease, nicotine use was found to be marginally protective of cardiovascular health compared to non-use of nicotine (139). This protective effect persisted even when adjusted for smoking status. Even within the ex-smoking sub-group in the same study, nicotine users had substantially lower rates of hospitalization then non-users. Nicotine also showed a marginally protective effect against peptic ulcer disease in the same subjects. In a long-term maintenance study of non-smoking patients with ulcerative colitis, there were no increased cardiovascular events and markers of cardiovascular risk either did not change or actually decreased (e.g. fibrinogen) (140). An investigation of the effects of 26 weeks of chronic oral nicotine showed improved cardiovascular risk parameters (e.g. capillary flow, fibrinogen) after smoking cessation with no negative effects of nicotine (141). Nicotine does not appear to promote thrombosis or platelet aggregation nor does nicotine replacement therapy increase the risk of acute myocardial infarction (DrugDex Drug Evaluation Monograph).

Studies of patients with known cardiovascular disease have similarly not shown an increase in cardiovascular events or toxicity secondary to nicotine therapy. Two large studies of men with documented coronary artery disease with up to 10 weeks of nicotine therapy showed lower rates of cardiovascular endpoints and events in the nicotine-treated group (142). A study of myocardial perfusion in men with coronary artery disease showed that cigarette smoking was associated with significantly greater myocardial perfusion deficits than nicotine therapy alone, suggesting that such a perfusion defect is due to factors from tobacco other than nicotine. In reviewing the available clinical trial literature and data reported to the FDA as of 1998, Rennard and colleagues

concluded: "the available clinical trial and the clinical experience reported to date are consistent with the relative safety of transdermal nicotine in stable patients with cardiac disease."

In our MCI study, an examination of change in systolic blood pressure revealed a significant reduction in systolic blood pressure compared to placebo treatment (Figure below). By day 182, the placebo group showed an average increase of 9.6 mmHg in SBP compared to a reduction of 4 mmHg in the nicotine-treated group. There was a small reduction in diastolic blood pressure by day 182 in the nicotine-treated group. An examination of the change in pulse showed no overall treatment effect (p = 0.51).



Safety Experience in Individuals with Cardiovascular Disease: The results of two controlled trials of NRT in patients with cardiovascular disease have been published (143,144). The first study was a 5-week, placebo-controlled trial of 14 to 21 mg/day of transdermal nicotine in 156 patients with stable coronary artery disease (143). Cardiac symptoms were recorded, and in a subgroup, 24-h ambulatory electrocardiographic (ECG) monitoring was performed before and during the first and last weeks of treatment. Of note, the quit rates were low, so there was much concomitant smoking and patch use in each group. Frequency of angina declined both in nicotine and placebo groups, with no difference between treatments. Ambulatory ECG monitoring revealed no differences in arrhythmias or ST segment depression changes in nicotine- versus placebo-treated patients. Plasma nicotine concentrations averaged 14.1 ng/ml with transdermal nicotine in those who did and 21.1 ng/ml in those who did not quit smoking. Joseph et al. (144) reported the results of a large Veterans Affairs cooperative study of 584 smokers with cardiovascular disease. Patients received a 10-week course of transdermal nicotine (beginning at 21 mg/day and tapering to 7 mg/day) or placebo. Many participants continued to smoke cigarettes. The incidence of primary end points (death, myocardial infarction, cardiac arrest and admission to the hospital for increased severity of angina, arrhythmias or congestive heart failure) was similar in both groups (nicotine group: 5.4%; placebo group: 7.9%). **These two studies** (143,144) **found no evidence of aggravation of coronary artery disease by NRT.**

An experimental study (145) further supports the safety of transdermal nicotine, even in the setting of concomitant cigarette smoking, in patients with severe coronary artery disease. Thirty-six male smokers with a baseline ≥5% reversible perfusion defect by quantitative thallium-201 single-photon emission computed tomography were treated with 14- and 21-mg nicotine patches sequentially. Despite instructions to stop, most continued smoking, although they smoked fewer cigarettes per day. In the setting of increasing plasma nicotine levels (average: 15.8 ng/ml at baseline, 24.2 ng/ml for 14-mg nicotine patches, 30.4 ng/ml for 21-mg nicotine patches), there was a highly significant reduction in total exercise-induced perfusion defect size (average: 17.5% at baseline, 12.6% for 14-mg nicotine patches, 11.8% for 21-mg nicotine patches). **No patient had a significant increase in myocardial ischemia while using nicotine patches**. The progressive reduction in defect size was most closely related to the reduction in the blood carboxyhemoglobin concentration, which had decreased as a consequence of smoking fewer cigarettes. This study (145) suggests that carbon monoxide or some other component of tobacco smoke rather than nicotine is most important in limiting myocardial nutrient supply in patients with coronary heart disease. In that the perfusion defect size is known to have predictive implications for future myocardial infarction or death, or both (146), this study (145) suggests that **treatment with transdermal nicotine is not hazardous in patients with coronary heart disease and may even reduce cardiovascular risk in continuing smokers if the smoking rate is reduced**.

In another study (147), nicotine replacement therapy was found to improve myocardial function. Thirty-six of the 40 enrolled patients had exercise SPECT at baseline and during treatment with at least 14-mg nicotine patches. These patients had an initial perfusion defect size of 17.5 +/- 10.6% while smoking an average of 31 +/- 11 cigarettes per day for 40 +/- 12 years. A significant reduction in the total perfusion defect size ($p < 0.001$) was observed from baseline (17.5 +/- 10.6%) to treatment with 14-mg (12.6 +/- 10.1%) and 21-mg

(11.8 +/- 9.9%) nicotine patches. This reduction occurred despite an increase in treadmill exercise duration ($p < 0.05$) and higher serum nicotine levels ($p < 0.001$). There was a significant correlation between the reduction in defect size and exhaled carbon monoxide levels ($p < 0.001$) because patients reduced their smoking by approximately 74% during the trial. **Nicotine patches, when used to promote smoking cessation, significantly reduce the extent of exercise-induced myocardial ischemia as assessed by exercise thallium-201 SPECT**.

Cerebrovascular Safety: Smoking is a preventable risk factor for ischemic stroke and some preclinical studies have suggested potential mechanisms by which smoking and/or nicotine might increase the risk of ischemic stroke (148-151). However, a large meta-analysis of 35 smoking cessation trials did not find any increased incidence of stroke in nicotine replacement therapy users (106).

Conclusion regarding cardio- and cerebrovascular safety: As the subjects to be enrolled in this study will be nonsmokers selected for the absence of unstable cardiovascular or cerebrovascular disease, we believe that the cardiovascular and cerebrovascular risk profile of transdermal nicotine in such patients is excellent.

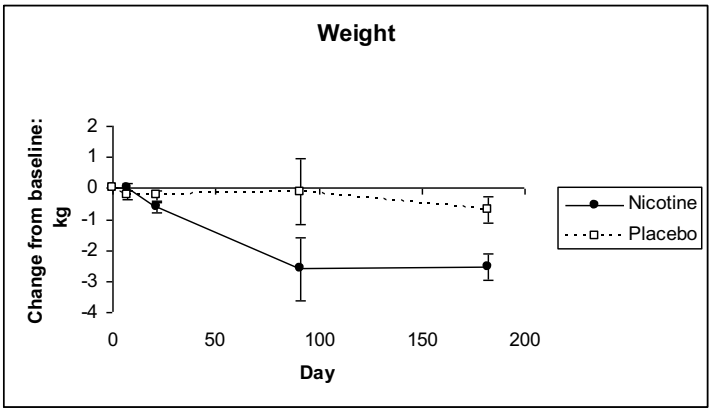
Insulin Sensitivity: There have been some epidemiologic studies suggesting a positive relationship between smoking and insulin resistance (152) although some studies are contradictory (153). Some investigations have suggested that changes in insulin sensitivity may be restricted to smokers who are also diabetic (154). Contradictory results were also seen in studies of smokeless tobacco use on cardiovascular risk factors and insulin levels with one study of heavy users finding impaired measures of glucose tolerance (155) while another study did not (156). At this point, it is not clear that nicotine use alone in nonsmokers is associated with changes in insulin sensitivity.

Carcinogenesis: Nicotine alone has not been shown to be carcinogenic. Long-term epidemiologic studies of oral tobacco use suggest that the nitrosamine content of tobacco is critical to determining the cancer risk from non- smoke related tobacco use, rather than nicotine (157). Whether nicotine can act as a permissive agent to encourage the development of cancer is unclear, but it does not seem to have any effect unless co-administered with tobacco (157).

Fetal Development: The FDA does not recommend the use of transdermal nicotine patches during pregnancy. Given how our age entry criterion (age 60 years or older) is concordant with a post-menopausal state, we will not require pregnancy testing.

Safety Experience in Older individuals: We have extensive experience in administering nicotine and novel nicotinic agonists to older patients with Alzheimer's and Parkinson's disease (158-160) . We have performed over 200 intravenous infusions of nicotine bitartrate salt to such patients with cardiac telemetry. No instances of cardiac ectopy or irritability have been seen and no other significant side effects other than nausea and/or vomiting have occurred. We have also administered nicotine by transdermal patch for four weeks to elderly patients with Parkinson's disease (161). Tolerability was excellent, even up to 22 mg nicotine patch per day. Only minor gastrointestinal upset was seen that was easily managed by dose reduction. No incidences of cardiovascular symptoms or difficulties occurred.

Chronic nicotine has been administered transdermally by other investigators to nonsmoking AD and PD patients in several studies for up to several weeks (161-165) without significant problems. No significant cardiovascular problems have been documented. Patients reported a vague feeling of lightheadedness, and some had mild behavioral changes.



Weight: In our recently published MCI study, examination of the change in body weight across visits showed that the nicotine-treated group showing

a significant decline in body weight by day 91 compared to placebo (-2.6 kg versus -0.1 kg for the placebo-treated subjects). However the nicotine-treated group stabilized and no further decline in weight occurred through day 182. We observed a similar pattern in our 12-week pilot trial in LLD. We will monitor weight over the course of the study.

Abuse Potential: We believe that the probability that the subjects in this study might be prompted by their participation to begin to use nicotine containing products or tobacco is extremely low. There have been no cases reported in the medical literature of primary abuse by never smokers of nicotine replacement therapies. Furthermore, there are no cases reported of ex-smokers taking up nicotine replacement therapy and becoming addicted or dependent. Additional reasons for our assertion that the risk of abuse of transdermal nicotine in this population is low include:

1) Nicotine replacement therapies have an extremely low abuse liability (166) . Nicotine patches have some unpleasant side effects and therefore are unlikely to be reinforcing.

2) Studies (167,168) show that experimental administration of tobacco does not induce ex-smokers to relapse into smoking. In another study (166), when non-smokers and ex-smokers were followed after participating in a study of nicotine gum administration, no subjects were found to be smoking or using other nicotine products three months following completion of the study.

3) An important characteristic of all drugs that produce dependency is the pharmacokinetic parameters associated with the route and form of administration (169). With respect to nicotine, researchers of the NIDA Addiction Research Center (170,171), as well as others in the field (172-175), have reported that the slower absorption of nicotine offered by the transdermal patch relative to tobacco products substantially reduces the likelihood of nicotine dependence in users of the patch. This was supported by a study describing a double-blind placebo-controlled study investigating the therapeutic potential of the transdermal nicotine patch for patients suffering from ulcerative colitis (140). Although all of the subjects were adults and many former tobacco users, despite 26 weeks of daily applications of 15 mg nicotine patches, no withdrawal symptoms were reported from these patients following discontinuation of the patch. In addition, a crossover trial evaluating the "liking" rating for the patch (22mg or 44 mg/24hr) in adults found no difference in scores between the active and placebo systems (176).

4) We have administered intravenous and/or transdermal nicotine and structurally related nicotinic agonists over the past 20 years to several hundred non-smoking subjects including young and elderly normal volunteers, patients with Alzheimer's disease, MCI, and patients with Parkinson's disease. We have not had a single subject take up tobacco use as a consequence of study participation. Perhaps most importantly, in our recently completed MCI trial, *no withdrawal symptoms were reported by subjects or informants* nor were any subjects reported to be continuing to use nicotine after the study was completed.

There are potential unknown risks related to transdermal nicotine patches.

Experience in Late-Life Depression: The majority of adverse events in our published pilot trial of 15 subjects with LLD were expected and concordant with what is described above. There were no SAEs and the most common adverse effects included nausea (N=7), dizziness (N=4) and headache (N=4). These were dose-limiting in 7 of the 15 subjects (including 1 early withdrawal). One participant reported a sharp increase in anxiety when increased from the 7mg patch to the 14mg patch. This anxiety resolved on lowering the dose. We observed no significant changes in blood pressure or heart rate but observed a decrease in weight (6.7lb, $t= 4.30$, $p<0.01$). We observed no ill effects or craving after tapering and discontinuing TDN over an additional 3 weeks.

RISK/BENEFIT RATIO: When the safety record outlined above is considered, the risks of participation in this study are low. The risks mainly consist of temporary side effects from the nicotine and/or the transdermal patch that do not constitute a serious danger when administered within a medical environment. Long-term

cardiovascular, cerebrovascular, and neurological safety of transdermal nicotine appears to be very favorable. Subjects may benefit from cognitive improvement and mood. The benefits to society of greater knowledge about the treatment of the cognitive changes in late-life depression and their possible amelioration, considering the human and economic costs of this disorder, would appear great. Overall the risk/benefit ratio appears to be in favor of conducting these studies.

12. RISKS – OTHER THAN STUDY DRUG

1. Diagnostic, Cognitive, and Clinical Interviews: Subjects may experience boredom or discomfort during the clinical interview and evaluations when discussing symptoms and recent life events. They may also experience frustration with some cognitive tasks. The study coordinators are experienced and skilled in interviewing depressed older adults. Should the subject wish to stop or take a break, the coordinator will allow it. Dr. Taylor or another study doctor will be available as a backup. Should the subject express **suicidal ideation** at any time during the interview, Dr. Taylor or another study doctor will be contacted immediately to assess the subject and to determine the appropriate course of action. **Thoughts of suicide will be taken very seriously**. Options for addressing this may include contacting the individual's outpatient mental health caregiver, referring for urgent psychiatric evaluation and treatment, or emergent evaluation and hospitalization. Similar practices will be used for other emergencies, including but not limited to psychosis, homicidal or violent thoughts, or an acute change in a subject's physical status.

   Safety Procedures for Telemedicine Evaluations: In context of the COVID-19 pandemic, we will allow some study procedures, including the initial screening visit, to be conducted at a distance using telemedicine approaches. If there are safety concerns, the study clinician can always require in-person visits instead of telemedicine visits. This is concordant with clinical practice in the Vanderbilt Department of Psychiatry and Behavioral Science that is using telemedicine for both new and established patient visits. We will follow their clinical guidance for this study.

   Prior to the screening visit, a study clinician will review the potential subject's Vanderbilt medical record. If there is a history of suicidality in the medical record, the visit will be conducted in person. For telemedicine visits (both screening and follow-up visits), at initiation of the visit we will obtain: 1) the address of the subject's location; 2) a phone number where the subject can be reached; and 3) the identity of any family members or friends at their location. This allows us to contact the subject if disconnected, but also to know where they are and who may be available to assist in case of an emergency. If thoughts of suicide arise during the interview, the patient will be directed to the Vanderbilt Psychiatric Hospital emergency Psychiatric Admissions Service for further evaluation. If a family member or friend is available, we will ask the subject for permission to share our concerns with them and enlist their assistance. We will then notify the Psychiatric Admissions Service about the expected arrival. If the subject is unable or unwilling to come to Vanderbilt or a local emergency room for evaluation, and a family member or friend is not available, we will contact the local police to detail our concerns and request a check on the subject's welfare. In either case, we will follow-up with the subject to assure their safety and disposition.

2. Magnetic Resonance Imaging: Although this procedure is generally low-risk, there are particular concerns. Individuals will be screened for the presence of implanted metal (including but not limited to medical devices, shrapnel, tattoos or permanent makeup); those who screen positive will be excluded from the study. Claustrophobia is also an issue for many potential subjects. During the MRI, subjects will have voice contact with a radiology technician, and may request the scan be stopped at any time.
   Another MRI-related risk is the occurrence of incidental findings on MRI. All scans are reviewed at time of acquisition and concerning findings are reviewed with an attending neuroradiologist. Should any concerning findings be seen, Dr. Taylor or another study doctor will convey these findings to the subject along with recommendations for further evaluation and facilitate referrals for such evaluation and treatment.

3. X-Rays: Occasionally there may be a concern on screening for MRI safety in individuals who may have past surgical histories or have been exposed to metal fragments. We will attempt to acquire medical records when possible, but may also obtain an x-ray when it is unclear whether or not there is implanted or

embedded metal. In these cases, if metal is found on x-ray and safety cannot be assured, the subject will be withdrawn. This will be an uncommon study procedure, but does involve exposure to a small amount of radiation. As this will be a single x-ray image obtained at one time point, this radiation exposure is of low risk.

4. Blood draw for levels of nicotine and nicotine metabolites: We will draw 10mL of blood to measure levels of nicotine and nicotine metabolites four times over the 12-week trial. This is a minimal risk procedure and amount. Risks involve mild discomfort, bruising, or bleeding. Blood will be drawn by a phlebotomist using sterile technique. Blood samples will be identified only by a subject ID number, initials (first and last) and date. They will be stored in a secured, locked, research-dedicated -70 degree freezer.

5. Worsening Depressive Symptoms: If individuals do not experience benefit with the patch, it is possible depressive symptoms would worsen and suicidal ideation develop. ***We are mitigating this risk*** by examining transdermal nicotine in an augmentation trial, so all participants will be on a stable therapeutic dose of a SSRI or SNRI antidepressant. We will safeguard against this risk by frequent monitoring and availability for phone calls or urgent in-person visits for worsening depression. If participants exhibit worsening depressive symptoms, they can withdraw or be withdrawn from the study and referred for appropriate clinical care. Similarly, the development of suicidal thoughts will result in study withdrawal and referral to the appropriate level of clinical care (outpatient, partial hospital, or inpatient).

6. End of Study Procedures: During the course of the study we will work with study subjects to identify providers who will continue their care at the end of the study. After completion of the 12-week final assessments, all subjects will undergo a three-week patch taper. They will then return for a final safety visit. We will then communicate to their physician about study procedures, their study participation, and if they benefited from their participation.

7. Breach of confidentiality: There is the potential risk of breach of confidentiality of clinical, genetic, and laboratory information. Dr. Taylor has extensive experience as a clinical investigator dealing with such sensitive information and have experience assuring that data is adequately protected. Safeguards to protect confidentiality include locked records and firewalls around password-protected electronic data, and all study data being coded, with the key linking the code with a subject's identity being kept in a separate, locked file accessible only to key study staff.

12. Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Subjects will be assessed for safety, medication tolerability, and unanticipated problems at each contact. Emergency contact information will be provided to each subject for urgent, unanticipated problems.

12.a. Definition of Adverse Events (AEs) and serious adverse events (SAEs). We define reportable non-serious adverse events as any adverse change in health or development of a side effect occurring in a study participant after enrollment. These may be expected events (known drug effects, as detailed in the consent form, safety monitoring plan, or package insert) or unexpected events. We define a SAE as any event that results in hospitalization, disability or permanent damage, is life threatening, results in death, or any other serious event that does not fit these outcomes but requires urgent medical intervention.

12.b. AE Monitoring and Reporting. All adverse events will be reviewed by Dr. Taylor and/or Dr. Newhouse approximately weekly as they occur. All AEs, regardless of being judged as related or non-related, will be summarized and included in the annual IRB continuing review. Unanticipated, non-serious AEs will be reviewed by Dr. Taylor and Dr. Newhouse. If felt to be likely related to study participation, we will consider whether they need to be added to the consent form. If so, we will submit them as an AE report and submit an amendment adding that risk to the consent form and other study documents.

12.c. SAE Reporting. All SAEs, regardless of whether they are determined to be related or not to study

procedures, will be reported to the Vanderbilt IRB within 7 calendar days of when study staff learn about the event. SAEs will also be reviewed jointly by Drs. Taylor and Newhouse to consider whether they need to be added to the consent form.

12.d. Data Safety Monitoring Board. As we will be using transdermal nicotine patches off-label in a different population than the approved indication, we will establish a DSMB for this study. The DSMB will consist of scientists including a geriatric psychiatrist, a geriatric internist, and a statistician. These individuals will be independent of and not include members of the study team. The DSMB will be named and the charter provided both to NIH and to the Vanderbilt IRB prior to initiation of study enrollment. It is anticipated the DSMB will meet every 6 months after initiation.

The DSMB, based on its review of the protocol, will work to identify the study-specific data parameters and format of the information to be regularly reported. All adverse events related to study medication and all severe adverse events and SAEs will be reported to the DSMB. The DSMB will convene to review these cumulative study medication related AEs, severe AEs and SAEs every 6 months while subjects are participating in the study.

DSMB reports will be provided to NIH and the Vanderbilt IRB at each continuing renewal.

Based on the review of safety data, the DSMB will make recommendations regarding the conduct of the study. These may include amending safety monitoring procedures, modifying the protocol or consent, terminating the study or continuing the study as designed.

13. STUDY WITHDRAWAL/DISCONTINUATION

Participants may withdraw from the study at any time. If participants leave the study early, we will recommend a medication taper and clinical referrals for further care.

A participant will be withdrawn from the study if:
1) The participant withdraws his or her consent
2) The PI considers it is in the best interest of the patient for him or her to stop study participation
3) In the PI's judgment, the participant's depressive symptoms have worsened significantly since study drug initiation
4) The patient develops suicidal ideation where he or she should be referred for regular clinical care for safety
5) The patient is lost to follow-up

14. SUBJECT REIMBURSEMENT

Participants may receive up to $600. Reimbursement is pro-rated for each visit:
- Screening Visit: $25
- Assessment visits with MRI (Weeks 0, 6 and 12): $150 / each.
- Clinic visits with blood draws but without MRI (Weeks 3 and 9): $50 / each
- Final safety visit (Week 15): $25

15. STATISTICAL CONSIDERATIONS

15.a. Data Management: All study data will be stored in a REDCap study database. The exception is for the raw and processed MRI scans that will be stored in the Vanderbilt XNAT Image Database system.

15.b Statistical Plan: After assessing normality, tests will be conducted as two-sided using alpha=0.05. If data are not normally distributed, we will either transform data or use nonparametric approaches. For this proof of concept study, no multiple comparison corrections will be used and results presented in that context.

Hyp 1A *(Target Engagement)*: TDN will enhance CCN function, measured as a reduction in the M/SFG Stroop BOLD response (the activation difference between incongruent and congruent conditions of the emotional Stroop task). 60% or more of subjects will exhibit a M/SFG z-score reduction of 0.5 or greater.

We will test for change in the difference in M/SFG ROI activation between the incongruent and congruent conditions of the emotional Stroop task. We will determine the signal difference between conditions and calculate the z-score change as detailed for our Go criteria (Sect C.10). Analyses will include all subjects regardless of final dose.

The primary outcome will be change in activation difference from baseline to week 12. This will be examined as both a continuous variable and a categorical variable, defined by our Go criterion of whether a subject exhibits a z-score reduction of at least 0.5 in M/SFG activity at 12-weeks. Change from baseline to week 6 and week 6 to week 12 are secondary outcomes. Analyses will include key covariates of age and sex. Exploratory analyses will examine the relationship between change in the M/SFG Stroop response and change in MADRS, using an approach similar to that described for the R33 phase, Hypothesis 2A, described in the R33 Phase Section 4.4, Statistical Design and Power.

Hyp 1B (*Exposure*): Higher nicotine exposure measured by dose or metabolite levels will be associated with a greater reduction in the M/SFG Stroop BOLD response.

Subsequent models will be structured as for Hyp 1A but include nicotine blood level exposure or final dose as explanatory variables. Primary analyses will examine 12-week change, with post-hoc analyses examining change from baseline to week 6 and week 6 to week 12.

To test for the association between the change in the Stroop BOLD response and the change in nicotine exposure across visits (baseline, week 6, week 12), we will employ a linear model in which change in activation will be the outcome variable and explanatory variables include change in blood nicotine level, visit time, and the interaction between change in blood levels and visit while adjusting for the effects of age and sex. The statistical significance of the regression coefficient associated with the interaction term is of primary interest to address the difference in the association between visits. Similar approaches will be used to examine dose.

For each visit, we will also examine contemporaneous correlation between change in the Stroop BOLD response and change in the steady-state plasma nicotine concentration or dose. Moreover, the prolonged effect of nicotine on the M/SFG Stroop BOLD response will be examined via lagged correlation, i.e., correlation between BOLD response at week 6 (or week 12) and blood level of nicotine at week 3 (or week 9). Finally, we will examine z-score change in the BOLD response as both a continuous and categorical measure based on meeting target engagement Go Criteria. Jointly, these analyses will inform R33 phase dosing.

Exploratory Analyses: Analyses of blood samples will provide levels of nicotine, cotinine, and the log 3-HC/cotinine ratio (a measure of nicotine clearance). We will examine whether nicotine or metabolite levels at week 3 predict subsequent dose-limiting effects. We will also examine how a **past smoking history** (defined as > 100 cigarettes over lifetime) or differences in antidepressant use (SSRI vs SNRI) is associated with target engagement, change in depression severity, or vulnerability to adverse effects.

15.c. Statistical Power: Per RFA MH-18-702, the R61 phase focuses on the preliminary evaluation of whether an intervention (TDN) modulates the target (M/SFG activity). In pilot data, 64% (7 of 11) of subjects met our neural circuit criterion for CCN engagement. Assuming that this is a reasonable estimate of the true proportion of individuals showing target engagement with TDN, N=30 produces a one-sided 95% lower-limit confidence interval with a lower bound of at least 0.5, i.e., a chance of 50% of participants meeting this criterion. The bootstrap distribution of the delta Z based on our pilot study further supports that we will have 80% power to detect at least 50% true positives, i.e., more than 15 out of 30 satisfy the delta Z $\leq$ -0.5 criterion.

16.0 PRIVACY/CONFIDENTIALITY ISSUES

16.a. Confidentiality Procedures: As the PI, Dr. Taylor will assure all procedures protecting study data designed to guard subject confidentiality conform to the Vanderbilt Human Research Protection Program requirements. All non-electronic data (clinical evaluations, paper assessments) will be stored securely in

locked offices or laboratories accessible only by study staff. All electronic data will be stored in secured servers with limited access. RedCAP will be used for data management.

Further, all information that could potentially directly identify a subject is removed from all study data. This includes MRI data, electronic and paper assessments. Direct identifiers will be replaced with a unique four-digit code. The key to linking the code to subject identity will be kept separately from study data, in a locked file in password-protected computer in Dr. Taylor's office. Only study staff involved in clinical recruitment and assessment will have access to individually identifiable private information. All other study staff, including image analysts, will be blinded to subject identity and will only have access to the coded identifier.

16.b. Privacy Procedures: Informed consent and all study procedures will occur in private research offices and private research examination rooms.

16.c. Creation of Global Unique Identifier (GUID): To facilitate NIMH-required data sharing described below, participants will be assigned a GUID using the GUID tool (https://nda.nih.gov/s/guid/nda-guid.html). The GUID Tool is software that accepts the personal information of subjects and uses it to create a series of hash codes. These codes are sent to the NIH system and checked against the GUID database. If these codes have been seen before, that means the information matches an existing GUID, and this GUID is sent back. If no match is found, a new GUID is created and sent back. If someone else enters the same information later, the tool will detect this match and send back the same GUID. The GUID itself is a series of alpha-numeric characters. With this system: 1) No personally identifying information ever leaves the institution's computers; 2) There is nothing about a GUID that would allow someone to infer the identity of the individual to whom it belongs; and 3) The same individual's information will result in the same GUID across time, location, and research study. This allows researchers to match shared data from that participant regardless of source, without ever sharing or viewing personally identifying information.

To create a GUID, at enrollment we will gather all of the following required information: sex, first name, last name, middle name, date of birth, and city/municipality of birth. In all cases, all of this information should be obtained and entered as it appears on the birth certificate. The GUID will serve as a secondary more complex coded identifier, in addition to the simpler primary 5-digit identifier. The GUID will be the only identifier used when sharing data outside of UIC, UPMC, and VUMC.

16.d. Transfer of Blood Samples for Analyses: Blood samples will be leaving Vanderbilt University Medical Center for analyses of levels of nicotine and nicotine metabolites by Dr. Rachel Tyndale at the Center for Addiction and Mental Health at the University of Toronto. These samples will be deidentified and include only the subject's study ID number, initials (first, last), and date of sample acquisition.

17. DATA SHARING

The proposed research will include clinical, cognitive, and neuroimaging data from older depressed subjects. The final dataset will also include sensitive clinical information about subject psychiatric diagnoses, psychiatric and medical history. Data will be deidentified and stored in REDCap and the Vanderbilt XNAT image storage database. Given our data safeguards we feel that subject identity will be protected.

We will also follow NIH guidance by planning to share data. These data will be shared with investigators working under an institution with a Federal Wide Assurance (FWA) and can be used for secondary study purposes. The names and Institutions of persons either given or denied access to the data, and the bases for such decisions, will be summarized in the annual NIH progress reports.

All data, the data dictionary, and technical details of assessments will be available for sharing and will be facilitated through our study data manager. All imaging data will have direct identifiers excised from the files prior to sharing. Data will be available for sharing as soon as possible but no later than within one year of the completion of the funded project period for the parent award or upon acceptance of the primary data for publication.

Given NIMH data sharing requirements and pursuant to NOT-MH-15-012, we will also share data via the National Institute of Mental Health Database (NDA) at the National Institutes of Health (NIH). The NDA provides a secure platform for data-sharing allowing for communication of research data, tools, and supporting documents. Data to be shared includes clinical data, cognitive data, and neuroimaging data gathered over the course of this study. No direct identifiers will be shared with the NDA and data coded using a GUID. Participants can refuse to have their data included in the NDA and still participate in the study.

18. FOLLOW-UP AND RECORDS RETENTION

Study records will be maintained for at least seven years after all study procedures are complete, all subject contact has ended, and the study is closed with the IRB. After that time, study data may be destroyed or anonymized, meaning all links to direct identifiers will be destroyed. Any study data in the medical record will be kept indefinitely.

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APPENDIX A: LIST OF ABBREVIATIONS

ACB	Anticholinergic Cognitive Burden
AD	Alzheimer's Disease
AE	**Adverse Event**
AES	Apathy Evaluation Scale
ASI3	Anxiety Severity Index 3
ATHF	Antidepressant Treatment History Form
BOLD	Blood Oxygen Level Dependent
CIRS-G	Cumulative Illness Rating Scale - Geriatrics
CCN	Cognitive Control Network
CPT	Continuous Performance Test
dACC	Dorsal Anterior Cingulate Cortex
DARS	Dimensional Anhedonia Rating Scale
dlPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
DSMB	Data Safety Monitoring Board
FIBSER	Frequency, Intensity, Burden of Side Effects Rating
FLAIR	Fluid-Attenuated Inversion Recovery
fMRI	Functional Magnetic Resonance Imaging
FSS	Fatigue Severity Scale
GAD	Generalized Anxiety Disorer
GAD7	Generalized Anxiety Disorder 7 item scale
GRSEB	Global Rating of Side Effect Burden
ISI	Insomnia Severity Index
LLD	Late-Life Depression
mAChR	Muscarinic Receptor
MADRS	Montgomery Asberg Depression Rating Scale
MCI	Mild Cognitive Impairment
MINI	Mini-International Neuropsychiatric Interview
MMSE	Mini-Mental State Exam
MRI	Magnetic Resonance Imaging
M/SFG	Middle / Superior Frontal Gyri
nAChR	Nicotinic Acetylocholiner Receptor
nAChRs	Nicotinic Acetylocholine Receptors
NDA	National Institute of Mental Health Database
PSWQ	Penn State Worry Questionnaire
SAE	Serious Adverse Event
TDN	Transdermal Nicotine
UPRTSO	Unanticipated Problem Involving Risk to Subjects or Others
VUMC	Vanderbilt University Medical Center
WHODAS 2.0	World Health Organization Disability Assessment Schedule 2.0

APPENDIX B: PROHIBITED MEDICATIONS

Antidepressants:

- Monoamine oxidase inhibitors (parnate, selegiline, etc)
- Tricyclic antidepressants (amitriptyline, nortriptyline, imipramine, desipramine, etc)
- Bupropion
- Paroxetine

Other Medications:

- Acetylcholinesterase Inhibitors
  - Donepezil
  - Galantamine
  - Rivastigmine

- Other anticholinergic drugs
  - Benztropine
  - Cyproheptadine
  - Diphenhydramine
  - Hydroxyzine
  - Meclizine
  - Promethazine
  - Oxybutynin

- CYP2A6 Inhibitors / Inducers (1)
  - Amiodarone
  - Bupenorphine
  - Clotrimazole
  - Disulfram
  - Fenofibrate
  - Ketoconozole
  - Letrozole
  - Miconazole
  - Modafinil
  - Tioconazole

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