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**Project Title: Nicotinic Treatment of Age-Related Cognitive Decline in Down Syndrome: An Open Label Pilot Trial**

**Statement of the Problem:** Over 50% of adults with Down Syndrome (DS) develop Alzheimer's disease (AD) by the age of 60 (Nadel 2003), and life expectancy in DS is now 50-60 years. Thus, age-associated cognitive impairment and dementia in older adults is an urgent public health concern. We propose that nicotinic stimulation is a promising strategy to stabilize or improve cognitive functioning in adults with DS, possibly with neuroprotective effects. We have extensive experience investigating the role of nicotinic receptors on human cognition and impairment. This application takes advantage of new insights into treating Mild Cognitive Impairment (MCI-the precursor condition to Alzheimer's Disease (AD) in typically developing individuals) with nicotine to propose an open label pilot study of transdermal nicotine in middle-aged non-smoking DS patients who show early cognitive and/or behavioral changes consistent with MCI/dementia. This study will ascertain whether nicotine is safe and tolerable in DS patients, help with dose-ranging of nicotine in DS, look for evidence of enhancements in cognitive functioning, and establish evidence for biological and behavioral correlates of nicotinic stimulation effects. Positive results on safety and cognitive or functional indices would lead to a proposal for a larger and longer double-blind trial. The knowledge gained from the translational aspects of this project may also guide the application of new nicotinic drugs in DS and generate, for the first time, data on the importance of nicotinic receptor changes in the development of cognitive impairment in DS adults.

**Specific Aims:** The goal of this study is to establish preliminary evidence for safety, gain preliminary evidence as to whether nicotine enhances cognitive functioning in DS adults, and examine electrophysiological, biological, and behavioral correlates of nicotinic stimulation effects.

**Research Questions:**

- Will nicotine be safe and well tolerated out to 1 month in middle aged DS patients with early cognitive changes?
- Will nicotine enhance laboratory measures of cognitive performance in adult DS patients with early cognitive changes (pre-post comparison)?
- Will nicotine treatment produce positive effects on functioning in DS subjects that are detectable by clinician and informant assessment?

Exploratory research aims:

- Examine effects on electrophysiologic markers of cognitive status, e.g. visual evoked potentials.
- Examine interactions between clinical, biological, and cognitive effects with genes such as APOE, CYP2A6, and other behavioral measures.

**Hypotheses:**

- Transdermal nicotine treatment will be well tolerated out to one month by non-smoking DS patients without significant adverse effects.
- Nicotine will enhance cognitive performance by one month compared to baseline and post-treatment testing.
- Nicotine will enhance functioning detectable by clinician and/or informant ratings (pre-post).

We propose that positive results on cognitive or functional indices that would lead to a larger and longer double-blind trial to test more definitively whether nicotinic stimulation may be cognitively and/or functionally enhancing for DS patients. The knowledge gained from the translational aspects of this project will guide the development of potentially new nicotinic drugs in DS and generate, for the first time, data on the importance of nicotinic receptor changes in the development of cognitive impairment in DS adults. This work also represents the first time that cutting-edge advances in treating MCI/AD in the general population are immediately and rigorously applied to those with DS.

**Introduction:** Down syndrome (DS) or trisomy 21, involves an extra copy of the gene for amyloid precursor protein (APP), located on chromosome 21. This leads inexorably to an increase in beta amyloid (Aβ) deposition with subsequent plaque and tangle development, the neuropathologic signature of Alzheimer's disease (AD). Despite having the requisite neuronal characteristics of AD, however, not all adults with DS develop the clinical manifestations of this disease. To date, only a few risk factors distinguish DS adults who do

or do not develop clinical symptoms. Similar to the general population, these risks include advancing age, reduced estrogen levels, elevated cholesterol, and the presence of the APOE4 allele (Zigman 2007).

In the general population, memory changes or mild cognitive impairments are early warning signs of dementia. In adults with Down syndrome, however, preclinical signs of dementia also include behavioral or personality changes, and such depressive symptoms as withdrawal, reduced communication, low mood, indifference, and passivity (Ball, Holland et al. 2006). Patients gradually develop progressive cognitive impairment beginning as early as age 40. A minority shows regression in adolescence or in the 20s, along with marked slowing and depression (Dykens 2012). At least 50% of adults develop an AD-like process culminating in dementia by the age of 60. AD develops in DS individuals with deficits in executive function, attention, and memory, with withdrawal and mood changes occurring earlier in the course of illness than in typical AD cases.

Adults with DS are living longer, with life expectancy moving from 10 years of age in the 1930's to 58 to 60 years in 2000 (Bittles 2002). Increased longevity is due to access to, and advances in, pediatric cardiac surgery, and improved medical treatments of respiratory infections and other comorbid conditions. As a result, age-associated cognitive impairment and dementia is becoming an increasingly pressing concern. The number of people with DS 40 years and older is expected to increase by 100% by 2045 (Larsen 2008). Already, the average age of the DS population in Scotland is 40 years, and in Australia, 75% of people with DS are 50 years of age and older (Torr J. 2010). Such large cohorts of aging adults add renewed urgency for effective treatments that prevent or slow age-related declines in DS. Only a few trials have examined anticholinesterase inhibitors (e.g., donezepil) or antioxidants (e.g., vitamin E) in DS adults with full-blown AD. Inhibitors show a modest slowing in disease progression (Prasher V.P. 2003). Ideally, however, treatments would improve or stabilize cognitive function *before* the onset of the disease, and be safe for long-term use, inexpensive and easily available. We propose that nicotinic stimulation may be a promising strategy to stabilize or improve cognitive functioning in adults with DS, possibly with neuroprotective effects.

**Rationale/Significance:** Central nervous system (CNS) nicotinic receptors are ligand-gated ion channels that chiefly serve to regulate the activity of presynaptic neurotransmitter release (e.g. acetylcholine, dopamine, etc.) on to postsynaptic receptors (Gotti 2004). Thus, activation of these receptors may act to amplify or regulate ongoing neural activity or to redirect or interrupt activity in the service of attention or cognitive functioning (Newhouse P.A. 2011). These receptors are widely distributed and are genetically diverse, with at least 12 genes controlling the expression of subunits that assemble to form several types of nicotinic receptors with differing pharmacologic properties. Nicotinic receptors appear to have several roles in normal human cognition, particularly in helping to regulate frontal and parietal attentional systems and medial temporal lobe memory processes(Newhouse, Potter et al. 2004). Loss of brain nicotinic receptors appears to be a hallmark of late stage AD, but relatively preserved in Mild Cognitive Impairment (MCI) or early AD. One particular subtype of nicotinic receptor (α7) appears to modulate APP and Aβ processing and thus, stimulation of this receptor may be neuroprotective. DS patients who suffer from dementia in late life may have involvement of these nicotinic receptors in AD-like brain changes (Deutsch 2004). One prior study showed evidence that a single dose of transdermal nicotine improved information processing in DS individuals (Seidl, Teifanthaler et al. 2000).

We have extensive experience investigating the role of nicotinic receptors on human cognitive function and the potential therapeutic benefits of nicotinic stimulation. We have shown that stimulating neuronal nicotinic receptors in Alzheimer's disease improves cognitive performance, while blocking neuronal nicotinic receptors impairs several cognitive domains and brain activity including attention, working memory, and episodic memory (Newhouse, Potter et al. 1994; Newhouse, Potter et al. 2001). Importantly, the shift in brain activity associated with blocking nicotinic and muscarinic cholinergic receptors during working memory replicates the pattern seen in cognitive aging (Newhouse P.A. 2011). Imaging data thus further demonstrate the importance of nicotinic receptors in age-related changes in attention and memory. We also find that stimulating nicotinic receptors improves behavioral inhibition and clinical status in Attention Deficit Hyperactivity Disorder (Potter and Newhouse 2008).

Recently, we completed a six-month, double-blind trial of transdermal nicotine for amnestic MCI, a precursor condition for AD (Newhouse, Kellar et al. 2012). In this study, 74 patients, with MCI were treated for six months in a double-blind, placebo-controlled design, with a six month open label extension. We found significant benefits of nicotinic stimulation. Statistically significant improvements were seen in measures of attention and memory in treated elders, as well as drug-related improvement in clinician- and patient-rated functional abilities. Safety was very good, even in elderly non-smokers, with excellent tolerability and no serious drug-related side effects or adverse events. Thus, transdermal nicotine improved cognitive performance and measures of clinical functioning in older patients with MCI.

Stimulation of nicotinic receptors with the canonical nicotinic agonist, nicotine, shows considerable promise for improving cognitive and functional symptoms in MCI/early AD, and it may also do so for similar stages in DS. The best time to treat cognitive impairment in individuals at risk for cognitive impairment is before severe symptoms of cognitive or memory loss becomes established. Since nicotine has not been given over this length of time to DS patients, we thus propose an initial open-label safety and efficacy trial of transdermal nicotine in adults with DS with early evidence of cognitive dysfunction.

**Methods:** We propose an initial, open-label pilot study (modified A-B-A design) of transdermal nicotine in middle-aged non-smoking DS patients who show early cognitive and/or behavioral changes consistent with developing MCI/dementia.

**Subjects:** Adults with DS (25+) who show early signs of cognitive dysfunction will be included. Individuals will be non-smokers, of either sex, and have no active cardiac or neurologic disease. They will be allowed to be taking most CNS active medication (e.g. antidepressants) as long as the doses of the medications are stable for at least three months. Patients taking antipsychotic or anticonvulsant medication will be excluded. Adults will be recruited using well-established community liaisons.
**Screening:** Cognitive dysfunction will be defined as "mild cognitive impairment" (MCI). MCI status will be based on cognitive tasks and informant reports that distinguish DS adults with or without cognitive concerns. Cognitive screening will utilize the Kaufman Brief Intelligence Test-II. The individually administered KBIT-2 was designed for research and screening purposes in individuals aged 4 through 90 years and has been successfully used in people with intellectual disabilities, and yields an overall Composite, Verbal and Nonverbal standard scores. (Kaufman, A.S., & Kaufman, N.L. 2004). In addition we will utilize the Arizona Cognitive Test Battery for Down Syndrome (Edgin et al, 2010), a battery specifically designed to identify and track cognitive deterioration in DS subjects. Informant instruments will include the Vineland Adaptive Behavior Scale, the Aberrant Behavior Checklist, and the Dementia Questionnaire. See detailed medical inclusion/exclusion criteria and medical screening procedures under “Human Subjects”.
**Treatment:** Following entry into the study, we plan a gradual titration of nicotine dose from low to at mid dose patches utilizing a daily nicotine patch worn for 16 hours per day beginning in the morning. Titration will begin by having the caregiver apply the patch 1 hour per day beginning at 8 AM, and gradually increasing treatment time by doubling the duration of the patch each day (1, 2, 4, 8, 16 hours) until 16 hours per day is reached. The patch will be removed at bedtime. The patch will be worn daily for 28 days, and then discontinued. Subjects will be assessed at baseline, Days 7 (safety only), 14, 28, and 42 (2 weeks post drug discontinuation).

Drug treatment schedule:

- Weeks 1 - 2: 7 mg per day (for 16 hours per day) gradually titrated as indicated above.
- Weeks 3 - 4: 14 mg per day (for 16 hours per day).
- Weeks 5 - 6: off treatment

## Study Visit Timeline

**Visit:**

| Screening | Day 0 | Day 7 | Day 14 | Day 28 | Day 42 |
|---|---|---|---|---|---|
| Consent/Assent | ERP Testing | | ERP Testing | ERP Testing | ERP Testing |
| Laboratory Testing Urine Pregnancy Test | | | | | |
| Medical History | Safety Assessment | Safety Assessment | Safety Assessment | Safety Assessment | Safety Assessment |
| Cognitive Screening | Cognitive testing | | Cognitive testing | Cognitive testing | Cognitive testing |
| | Informant and Clinician Global Assessment | | Informant and Clinician Global Assessment | Informant and Clinician Global Assessment | Informant and Clinician Global Assessment |
| | Low Dose Patch Application and Titration | | Mid Dose Patch Application | Discontinue Patch | |

**Outcome Measures:**

**Cognitive Assessment:** We plan to assess cognitive functioning with computerized and noncomputerized tests known to be sensitive to nicotinic effects at baseline, 2 weeks week, and one month after beginning treatment as well as 2 weeks after treatment has been discontinued. Neuropsychological tests geared for DS will specifically be used. The cognitive battery will take approximately 45 minutes for subjects to complete.

Primary Performance:

- **Continuous Performance Task (CPT).** Participants see a series of colored objects appearing one at a time on a computer screen. Stimuli appear for 300 msec with a response period of 2 sec for a total of 120 trials. Subjects are instructed to press a button whenever a particular colored object appears on the computer screen.
- The **Critical Flicker Fusion** (**CFF**) task (Kupke and Lewis 1989) will be used as a test of attention and vigilance. In an ascending trial, the participant presses a button indicating when the frequency of flashing lights, (beginning at 12 Hz and increasing to 50 Hz), has increased to the point that the lights appear to be no longer flashing but rather appear continuously on ("fused"). In a descending trial, beginning at 50 Hz, the participant presses a button when the frequency of apparently fused lights is decreased such that lights begin to appear to be flashing. The participant needs to respond before the frequency hits the upper or lower limit in each trial.
- **Choice Reaction Time** (CRT) task as modified from the Milford Test Battery will be used to examine psychomotor speed and response time. This version of the CRT allows total reaction time to be broken down into recognition and motor components (Hindmarch 1984).

Secondary Performance:

- **Verbal recall** including immediate, delayed, and forgetting utilizing a modified Selective Reminding Task with individualized baselines established by pre-testing.
- **Measures of impulsivity** including the Stop Signal Reaction Time task (SSRT) and the Balloon Analog Risk Task (BART). For the SSRT, we will use a modified/children's version of the stop signal and perform a longer training and begin with a shorter delay than the standard 250 msec that is typical for this task to make the task easier.
- **Executive Function:** 4 Trails Conditions from the Dellis-Kaplan Battery.
- **Event-related potentials (ERP)** - a brief temporary change in the EEG in a response to a stimulus - have long been used as a non-invasive tool to examine brain functioning (Russeler et al., 2005; Proverbio & Zani, 2003; Zani & Proverbio, 2003). Variations in ERP peaks are interpreted to reflect speed (latency) or degree (amplitude) of information processing. In addition to the excellent temporal sensitivity, ERPs reflect cognitive functioning even in the absence of overt verbal or motor behavioral responses, which makes them especially valuable for use in persons with limited ability to provide a reliable overt behavioral response, difficulty comprehending instructions, or other issues that make traditional behavioral assessments difficult to complete. We will utilize two tasks previously used to assess memory- and learning-related processes in typical aging populations and that have been successfully used in DS:

    - **Novelty detection** (Oddball) task (modeled after Daffner et al, 2006; Jeon & Polich, 2001): *Stimuli*: The stimuli will include 3 categories: (1) a standard stimulus (a blue triangle), 70% frequency; (2) a target stimulus (an upside down blue triangle), 15% frequency; and (3) novel stimuli - meaningless line drawings shown only one time each, 15% frequency. *Procedure*: All stimuli will be presented in random order for 500 ms in the center of a computer monitor 80 cm in front of the participant. The inter-stimulus interval will vary randomly between 1000-1300 ms to prevent habituation to stimulus onset. Participants will be instructed to view the stimuli but no behavioral response will be required. The entire recording will include 200 trials and will last approximately 10 minutes. *Variable of interest*: Amplitude and latency of the P3 responses to target and novel stimuli.

    - **Repetition detection** (modeled after Jessen et al., 2002): *Stimuli*: Fifty unfamiliar pictures and a drawing of a yellow smiley face will serve as the stimuli. The unfamiliar stimuli will be 50 color

photographs of complex indoor and outdoor scenes, including pictures of objects and animals but excluding pictures of human faces. Ten of the unfamiliar pictures will be randomly selected and repeated five times throughout the experiment, yielding 50 repeated pictures. To keep the attention focused, a picture with a smiley face will be presented 18 times throughout the session (brain responses to this stimulus will not be included in the analysis). *Procedure*: All stimuli will be presented in random order for 1500 ms with a random inter-stimulus interval of 1300-1600 ms. Participants will be asked to press a response button when they see the smiley face. The entire task will include 118 trials and will last approximately 7 minutes. *Variable of interest:* Change in ERP responses to repeated pictures over the recording time (e.g., first 25 trials vs. last 25 trials).

**Clinical Measures:**

- Primary Clinical:
  Global rating scale for DS: The Dementia Scale for Down Syndrome (Gedye, 1995) is an informant based rating scale designed to give a global assessment of cognition and functioning in DS individuals.
- Secondary Clinical:
  Outcomes will also include structured caregiver and clinician assessments of adaptive functioning and problem behaviors including the Aberrant Behavior Checklist (Brown et al, 2002). This scale examines maladaptive behaviors in 5 domains: Irritability, Lethargy/Withdrawal, Stereotypic Behavior, Hyperactivity, Inappropriate Speech. The Vineland Adaptive Behavior Scales-II (Sparrow, Cicchetti, & Balla, 2005 is a semi-structured interview with parents or informants that identifies the performance of behaviors required for personal or social self- sufficiency.

**Safety Measures:** At the screening day, a CRC nurse will collect vital signs and specimen samples (urine) for Urinalysis. An ECG will be performed, and participant and caregiver will answer a comprehensive questionnaire at every study visit (Day 7, Day 14, Day 28, and Day 42) to assess any side effects or adverse events resulting from study medication.

All participants will be expected to progress to the 14mg dose after the second week of the study, provided they are tolerating the medication. However, participants who experience persistent nausea, vomiting and dizziness at the 7mg dose (indicating that the higher dose will not be tolerated) will not progress to the 14mg dose.

**Compensation:** Caregivers/guardians will be reimbursed for their time and trouble at $250 for the entire study prorated at $50 per visit. In addition reasonable travel expenses will also be reimbursed. Subjects will be offered a Visa gift card for their compensation for participation.

**Data Analysis/Power Calculation:**
This is primarily an open-label safety and tolerability study; thus, statistical analysis of data is mostly descriptive. Tabulation of safety information, examination of vital signs changes over time, and preliminary examination of cognitive performance and global ratings over time will be the primary analytic approach.

**Safety Outcome**: Tolerability and safety will be determined by counting specific adverse events, counting dropouts due to adverse events, and by determining how often there is a need to reduce the dose of nicotine as determined by the participant/caregiver and the physician. Abnormalities in vital signs, physical examination, and laboratory tests will be collected by treatment. Adverse events will be recorded and categorized by body system, event type, attribution, frequency, severity, and course. Changes in vital signs will be assessed using one-way repeated-measures ANOVA with time as the within-subjects factor.

**Cognitive Performance:** Comparison of the baseline (Day 0) with Day 28 will be performed with paired t-tests. One-way ANOVA may be used to assess the effect of change in performance over time (0, 14, 28, 42 days). Significant improvement from baseline and/or loss of effect after treatment withdrawal (effect of time) will be considered a positive result.

**Behavioral/Functional Assessments:** Comparison of the baseline (Day 0) with Day 28 will be performed with paired t-tests for the behavioral scales as in the analysis of the cognitive performance battery. Individual items and totals of the behavioral measures will be compared descriptively.

**Global Ratings:** Analysis will compare global ratings for nicotine treatment examining baseline vs end of treatment study (paired t-test), and 2-week post treatment ratings. Age, APOE and CYP2A6 genotype, and

cognitive scores at baseline may be examined for influence on results.

**Sample Size:** Sample size calculations are challenging for an open label tolerability and cognitive feasibility study. However, in the Seidl study of a single dose of nicotine in DS patients, significant results on ERP measures were seen with as few as 4 patients. Considering that we are administering the medication for a longer period of time with multiple testing sessions, we feel based on prior studies with nicotine and nicotine patch (e.g. in our Parkinson's disease study), that a sample size of 15 enrolled to obtain a final cohort of 10 subjects is appropriate for testing initial safety, dose-ranging, and feasibility.

**Human Subjects:**

**SUBJECT SELECTION AND EVALUATION:** Initial screening of recruited subjects will be performed by the Study Coordinator. If a subject passes screening, he/she will be brought in for initial medical evaluation that will be performed by a Nurse Practitioner or physician. At baseline, a complete medical history and physical exam will be performed to ensure good general health. Medical history will be obtained from the informant and available medical records. Information on allergies, all current medications, and present and past use of tobacco, alcohol, and illicit drugs will be collected. Subjects cognitively and behaviorally screened by the psychometrist as described below. Laboratory and electrocardiogram screening will take place on the GCRC or OP clinic. The detailed screening packet including medical history, physical and neurological examination, laboratory testing, ECG, cognitive testing, behavioral screening, and consent form will be reviewed by the principal investigator for approval prior to study entry.

Diagnosis of Mild Cognitive Impairment: The criteria for the diagnosis of MCI used in this study with DS patients will consist of the following criteria similar to the criteria for amnestic MCI (Petersen et al. 2001):

1. Declining cognitive function corroborated by an informant.
2. Impaired memory function compared to prior testing.
3. Preserved general cognitive function.
4. Generally intact activities of daily living.
5. Not demented.

Specific Inclusion and Exclusion criteria:

Inclusion:

1. Cognitive complaints and/or memory difficulties which are verified as new onset by an informant.
2. Cognitive Global Rating consistent with mild impairment or deterioration from premorbid baseline.
3. General cognition and functional performance sufficiently preserved such that a diagnosis of Alzheimer's disease/dementia cannot be made by the physician at the time of the screening visit.
4. No significant cerebrovascular disease: Modified Hachinski score of less than or equal to 4.
5. Age 25+.
6. Stable medications for at least 1 month prior to screening. CNS medications should be stable for 3 months.
7. No evidence of major depression.
8. Informant is available who has frequent contact with the subject (e.g. an average of 10 hours per week or more).
9. Adequate visual and auditory acuity to allow neuropsychological testing.
10. Good general health with no additional diseases expected to interfere with the study..
11. ECG without clinically significant abnormalities that would be expected to interfere with the study.
12. Subject is not pregnant, lactating.
13. Subjects will be taking no drugs with cholinergic properties (e.g donepezil).
14. Agreement not to take other vitamin or supplements other than multivitamins.
15. Negative urine pregnancy test in females.

Exclusion:

1. Any significant neurologic disease such as Alzheimer's disease, Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic deficits or known structural brain abnormalities.

2. Major depression or another major psychiatric disorder as described in DSM-IV.
3. History of alcohol or substance abuse or dependence within the past 2 years (DSM IV criteria).
4. Any significant systemic illness or unstable medical condition which could lead to difficulty complying with the protocol including:
    a) History of myocardial infarction in the past year or unstable or severe cardiovascular disease including angina or CHF with symptoms at rest.
    b) Clinically significant obstructive pulmonary disease or asthma.
    c) Clinically significant and unstable gastrointestinal disorder such as ulcer disease or a history of active or occult gastrointestinal bleeding within two years.
    d) Clinically significant laboratory test abnormalities on the battery of screening tests (urinalysis, ECG).
    e) Insulin-requiring diabetes or uncontrolled diabetes mellitus.
    f) Uncontrolled hypertension (systolic BP> 170 or diastolic BP> 100).
5. Use of any investigational drugs within 30 days or 5 half-lives, whichever is longer, prior to screening.

Subjects with major concomitant illnesses will be excluded on the basis of history, physical exam, and laboratory tests assessing cardiovascular and renal function. ( U/A, ECG).

**Cognitive Screening:** This will use the Kaufman Brief Intelligence Test-II (KBIT-2). The individually administered KBIT-2 was designed for research and screening purposes in individuals aged 4 through 90 years and has been successfully used in people with intellectual disabilities, and yields an overall Composite, Verbal and Nonverbal standard scores. (Kaufman, A.S., & Kaufman, N.L. 2004). In addition we will utilize the Arizona Cognitive Test Battery for Down Syndrome (ACTB) (Edgin et al, 2010), a battery specifically designed to identify and track cognitive deterioration in DS subjects. The ACTB includes neuropsychological assessments chosen to assess a range of skills and be non-verbal so as to not confound the neuropsychological assessment with language demands. The ACTB includes tests of general cognitive ability and prefrontal, hippocampal and cerebellar function. Finally, we will use the Dementia Scale for Down Syndrome (DSDS) (Gedye, 1995). The DSDS is a 60-item informant-based instrument that was designed to aid in diagnosing dementia in individuals with intellectual disability, especially those with DS. The DSDS can also be used to establish a baseline measure on individuals with ID who are at risk of developing dementia because of their age, but currently do not exhibit signs of cognitive decline.

**Behavioral screening** will consist of the Aberrant Behavior Checklist (Brown et al, 2002). This scale examines maladaptive behaviors in 5 domains: Irritability, Lethargy/Withdrawal, Stereotypic Behavior, Hyperactivity, Inappropriate Speech. In addition, the Vineland Adaptive Behavior Scales-II (Sparrow, Cicchetti, & Balla, 2005) is a semi-structured interview with parents or informants that identifies the performance of behaviors required for personal or social self- sufficiency.

At the end of the screening process, the principal investigator will review all the screening information collected and verify that the subject meets criteria for the study and that the subject's general cognitive and functional performance is sufficiently preserved such that a diagnosis of Alzheimer's disease cannot be established at the time of the screening evaluation.

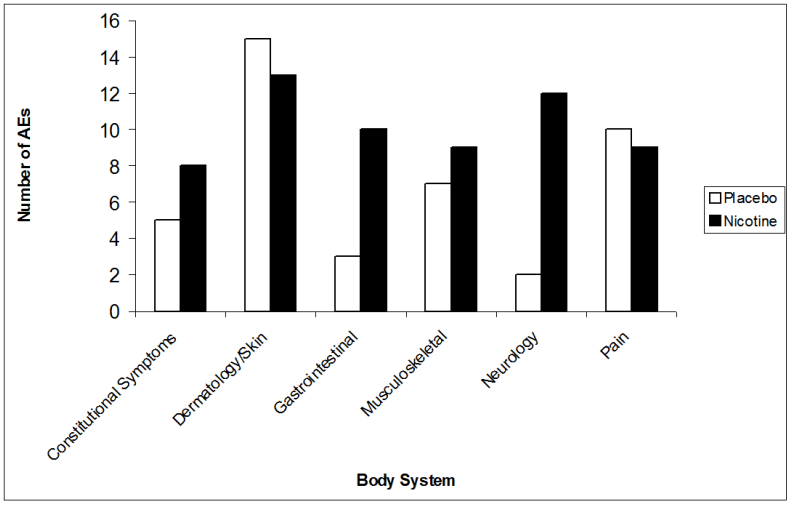
CONSENT/ASSENT: It is assumed that all subjects in this trial will have a legal guardian. Informed consent (from the guardian) and assent (from the subject) will be obtained by the investigators. Each subject and his/her guardian will receive an oral and a written explanation of the purposes, procedures and potential hazards of this study. A record of the communication of this information and the subject's assent and guardian 's (if appropriate) informed consents will be entered into the subject's medical record. Each MCI patient will be individually assessed by the investigators for ability to give assent/consent. Criteria for assessing this capacity will be those of the President's Commission for the Study of Ethical Problems in Medicine (The Presidents Commission for the Study of the Ethical Problems in Medicine and Biomedical and Behavioral Research 1982). Guidelines developed at the NIH Clinical Center for consent with impaired subjects (Fletcher and Wichman 1987) will also be followed for the involvement of family members in the consent process.

## POTENTIAL RISKS/DRUG SAFETY: NICOTINE TRANSDERMAL PATCH

**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 (Greenland, Satterfield et al. 1998)(Greenland et al. 1998). 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 recently published MCI trial [REF], 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 (4) discontinued treatment for adverse events than placebo-treated subjects (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 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 (Spyker, Alderfer et al. 1998). These effects consist of erythema, pruritus, edema, and rash. Mild

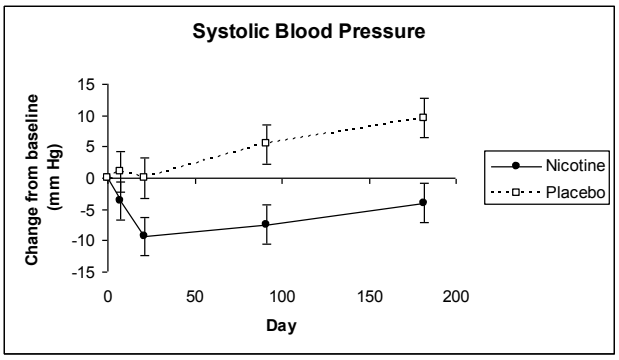
skin irritation is common and generally occurs after three weeks of continuous use. Mild to moderate reddening of the skin is seen in 25% of subjects and transient itching in 29%. More severe reactions requiring modification of treatment have been reported in up to 12% of users (DrugDex Drug Evaluation 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. The PI 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 (Benowitz 1998). Nicotine stimulates CNS sympathetic systems and increases release of catecholamines from both the adrenal and vascular nerve endings. While tolerance appears to develop to these cardiac stimulatory effects, the tolerance developed is only partial (Benowitz 1998a). While there may be a small chronic cardio-stimulatory effect (approximately seven beats per minute), the dose response curve appears to be flat (Benowitz 1998).

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 (Murray and Daniels 1998). 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) (Rhodes, Green et al. 1998). A recent 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 (Haustein, Haffner et al. 2002). 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 (Rennard, Daughton et al. 1998). 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."

**MCI Study:** An examination of the 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 ($p = 0.51$).




**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 (Gerzanich, Zhang et al. 2001);(Hawkins, Brown et al. 2002);(Zidovetzki, Chen et al. 1999). However, a large meta-analysis of 35 smoking cessation trials did not find any increased incidence of stroke in nicotine replacement therapy users(Greenland, Satterfield et al. 1998).

Conclusion regarding cardio- and cerebrovascular safety: As the subjects to be enrolled in this study will be nonsmokers selected for the absence of significant cardiovascular, cerebrovascular disease, or diabetes, 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 (Mikhailidis, Papadakis et al. 1998) although some studies are contradictory (Henkin, Zaccaro et al. 1999). Some investigations have suggested that changes in insulin sensitivity may be restricted to smokers who are also diabetic (Targher, Alberiche et al. 1997). One study that did examine long-term nicotine use without cigarette smoking showed that nicotine gum users had higher circulating leptin levels that were negatively correlated with the degree of insulin sensitivity (Eliasson and Smith 1999). However, the subjects were also recent ex-smokers, complicating interpretation of these results and acute administration of nicotine during the study did not change circulating leptin levels. 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 (Persson, Carlsson et al. 2000) while another study did not (Eliasson, Asplund et al. 1995). At this point, it is not clear that nicotine use alone in nonsmokers is associated with changes in insulin sensitivity.

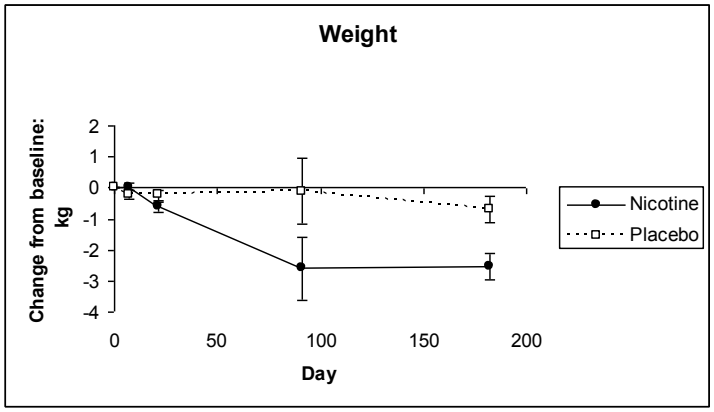
**Carcinogenesis:** Nicotine alone has not been shown to be carcinogenic. Long-term epidemiologic studies of oral tobacco use suggest that the nitrosamine content of tobacco is critical to determining the cancer risk from non- smoke related tobacco use, rather than nicotine (Benowitz 1998). Whether nicotine 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 (Benowitz 1998).

**Safety Experience in Cognitively Impaired individuals:** We have extensive experience in administering nicotine and novel nicotinic agonists to patients with Alzheimer's and Parkinson's disease (Newhouse, Sunderland et al. 1988);(Newhouse, Potter et al. 1996);(Potter, Corwin et al. 1999) . 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 (Kelton, Kahn et al. 2000).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 (Fagerstrom, Pomerleau et al. 1994; Parks, Young et al. 1994; Katayama, Hirata et al. 1995; Wilson, Langley et al. 1995; Kelton, Kahn et al. 2000) without significant problems. No significant cardiovascular problems have been documented. In the Wilson study, a 22 mg nicotinic patch was given to elderly demented AD patients continuously for 8 days without significant side

effects. Effects of the patch included 5 beat-per-minute increase in heart rate (average over 24 hrs), and mild increase in ectopy (ventricular ectopics increasing from 0.40-0.54%). There was, however, no ischemia or nausea. Patients reported a vague feeling of lightheadedness, and some had mild behavioral changes (belligerence and non-compliance).

**Weight:** In our recently published MCI study [REF], 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 -.11 kg for the placebo-treated subjects). However the nicotine-treated group stabilized and no further decline in weight occurred through day 182.




**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 belief that the risk of abuse of transdermal nicotine in this population include:

1) Nicotine replacement therapies have an extremely low abuse liability (Hughes, Strickler et al. 1989) . A recent study showed that non-smoking adolescents (the most vulnerable group to smoking initiation) are extremely unlikely to be interested in taking up nicotine replacement therapies because of the easier availability of cigarettes as opposed to over-the-counter nicotine replacement therapies (Adams, Korberly et al. 2001). Surveys from almost 200,000 high school students from a representative sample of 200 schools in eight geographic regions of the U.S. showed very little use of nicotine replacement therapies. Seventy-five to 80 percent of students who had tried the nicotine patch used it only a few times. Daily use of the patch range from 0.07 to 0.1 percent and use was for the most part experimental. Investigators concluded that the prevalence of the use of these products was so low that the hypothesis that the nicotine replacement patch or spray might act as a "gateway drug" did not seem tenable.

2) Nicotine patches have some unpleasant side effects and therefore are unlikely to be reinforcing. The administration will be blinded.

3) A study by Fertig (Fertig, Sayler et al. 1982; Seyler Jr., Pomerleau et al. 1986) showed that experimental administration of tobacco did not induce ex-smokers to relapse into smoking. In another study (Hughes, Strickler et al. 1989), 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.

4) An important characteristic of all drugs that produce dependency is the pharmacokinetic parameters associated with the route and form of administration (Farre and Cami 1991). With respect to nicotine,

researchers of the NIDA Addiction Research Center (Henningfield and Keenan 1993), as well as others in the field (Pomerleau 1992);(Marks, Stitzel et al. 1987);(Rose, Westman et al. 1996);(Shytle, Silver et al. 1996), 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 (Rhodes, Green et al. 1998). 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 (Bunker, Pickworth et al. 1992).

5) We have administered intravenous and/or transdermal nicotine and structurally related nicotinic agonists over the past 17 years to several hundred non-smoking subjects including young and elderly normal volunteers, patients with Alzheimer's disease, and patients with Parkinson's disease. We have not had a single subject take up tobacco use as a consequence of study participation.

6) In studies treating adolescents with Tourette's Syndrome with nicotine patches, researchers reported no known cases of participants craving nicotine or beginning to smoke following exposure to transdermal nicotine as part of a research treatment protocol. Specifically, none of the children with Tourette's Syndrome who had been treated repeatedly (19 days) with the transdermal nicotine patch reported that they felt "addicted to" or "craved" the nicotine patch when it was discontinued (Shytle, Silver et al. 1996).

7) A recent trial of transdermal nicotine has been conducted in children with ADHD (Shytle, Silver et al. 2002) utilizing transdermal nicotine patch in 10 children (mean age of 10) for a one-week period. While some expected nicotinic side effects occurred during the acute trial (e.g. nausea), no tobacco use or nicotinic product abuse has been seen in these children thus far in follow-up.

8) 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.

The safeguards that we have instituted that are described above taken in conjunction with data documenting that the administration of nicotine via non-tobacco routes is not associated with abuse liability, suggests that the incremental additional risk to subjects for tobacco use over and above their background use rate is likely to be very small.

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 delay in progression of the dementia associated with DS. The benefits to society of greater knowledge about the treatment of the cognitive changes associated with pathologic aging in DS 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.

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