Nicotine Therapeutics: Treatment of Disorders of the Aging Brain with Nicotinic Stimulation

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Cognitive Changes with Normal/Pathologic Aging Relevant to Cholinergic System Activity

- Decline in speed of processing (*Salthouse*)
- Decline in unisensory functioning and increased dependence on multisensory integration (*Wallace*)
- Difficulties in controlling the focus of attention (*Hartman and Dumas*)
- Reduction in HERA (hemispheric encoding/retrieval asymmetry) (*Tulving*); shift towards bilateral encoding/retrieval (*Cabeza*)
- Shift in activation from caudal to frontal (PASA effect) (*Grady, Langenecker, Cabeza*)

**Resource Reduction**
Brain Cholinergic System

Muscarinic Receptors

- M₁
- M₂
- M₃
- M₄
- M₅

- CNS
- Heart
- Smooth muscle
- CNS

Acetylcholine (ACh)

ACh receptors

- Nicotinic receptors
- Muscarinic receptors

Nicotinic Receptors

- Heteromeric nAChRs
- α4β2
- α4α6β2β3
- α3β4
Cholinergic System and Cognitive Functioning

**Top-down and Bottom-up Regulation of Attention**

- Practically all cortical neurons are innervated by ACh.
- All cortical information processing is modulated by cholinergic input.
- Cholinergic system activation affects performance on resource demanding tasks that require the allocation of attention.
- *Decline in the integrity of the cholinergic system results in robust and persistent impairments in attention and memory.*

Components of the cholinergic modulation of input processing or signal detection

Resource Decline in Cognitive Aging: Cholinergic Compensation Model

Dumas and Newhouse 2011
Age and MCI/AD Impact the Cholinergic Basal Forebrain

**Structural Change**

**Functional Change:** A gradient of severity of the cortical cholinergic denervation

- A) healthy control
- B) mild AD
- C) severe AD

Grothe et al, 2012

Aghourian et al 2017
Loss of Nicotinic Cholinergic Receptors in Alzheimer’s Disease

Reduced 2-FA binding; Controls > AD

Okada et al, Brain 2013

Sulzer et al, AJGP 2017
Alzheimer’s Disease Progression May Lead to Nicotinic Receptor Dysfunction

Prodromal AD or MCI: nAChR transient activation via Aβ monomers

AD: nAChR block or dysfunction via Aβ oligomers

Dinely et al, 2015
Blocking Nicotinic Receptors Impairs New Learning With Increasing Sensitivity with Age and Disease

Blockade of nicotinic receptors impairs attention, psychomotor functioning, working and episodic memory.

- Newhouse et al, Neuropsychopharmac 10: 93-107, 1994
Nicotinic Blockade with Mecamylamine Dose-Dependently Impairs Verbal Learning

Selective Reminding Task

Elderly normals vs AD patients

* p < .05

Newhouse et al, 1996
Neural Signature of Brain Compensation in Normal Aging: Posterior to Anterior Shift in Cortical Activity (PASA)
Reproducing the Aging Phenotype with Nicotinic Antagonist Cortical Activity During Working Memory

Nicotinic blockade (with mecamylamine) increases and shifts cortical activity during working/episodic memory: *Reproducing the PASA Effect.*

Mecamylamine increases activity in memory-relevant areas for retrieved words compared to encoded words ($p < .01$).

- Increased activation after mecamylamine in the inferior temporal gyrus, anterior hippocampus, occipital lobe, and the uncus.

- This memory task allowed for dissociation of encoding and retrieval processes during nicotinic system manipulation.

Newhouse et al, Biochem Pharm 82 (2011) 943–951
Increased Task-Related Brain Activity in Older Women with Subjective Cognitive Impairment: Need for Greater Resources

The shift in task-related cortical activity may represent cognitive compensation in aging secondary to cholinergic receptor-based systems.

Activation map for cognitive complainers (CC) minus noncomplainers (NC) as working memory load was parametrically increased from 0-back to 3-back (p < 0.005).

Dumas and Newhouse, Neurobiol Aging, 2012
Evidence that Acute Nicotinic Stimulation Improves Cognitive Performance in Late-Life Cognitive Disorders

**Acute nicotinic stimulation** improves Long-Term Verbal Recall in patients with early Alzheimer’s Disease

- Newhouse et al, Psychopharm 95: 171-175, 1988
- Potter, Newhouse et al, Psychopharm, 142: 334-342, 1999
Evidence that *Chronic* Nicotinic Stimulation Improves Cognitive Performance in Late-Life Cognitive Disorders

Subchronic nicotine improves performance and clinical ratings in AD/AAMI patients

Pilot Trial of Chronic Transdermal Nicotine for Symptomatic Improvement in MCI

Questions:

- Is transdermal nicotine safe and tolerable over extended periods in non-smokers?
- Does transdermal nicotine produce cognitive and symptomatic improvement in amnestic MCI subjects?

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<th>Demographics</th>
<th>Nicotine (N=39)</th>
<th>Placebo (N=35)</th>
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<td>Gender</td>
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<td>Male (N=45)</td>
<td>25 (64%)</td>
<td>20 (57%)</td>
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<td>Female (N=29)</td>
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<td>Age</td>
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<td>75.1</td>
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<tr>
<td>Weight (kg)</td>
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<td>73.9</td>
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<tr>
<td>Education</td>
<td>15.6 (2.9)</td>
<td>16.2 (2.4)</td>
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<thead>
<tr>
<th>Genetics</th>
<th>Nicotine (N=39)</th>
<th>Placebo (N=35)</th>
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<tbody>
<tr>
<td>ApoE4 Genotypes (N=70)</td>
<td></td>
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</tr>
<tr>
<td>ApoE4 present (N=30)</td>
<td>14 (38%)</td>
<td>18 (51%)</td>
</tr>
<tr>
<td>ApoE4 absent (N=40)</td>
<td>23 (62%)</td>
<td>17 (49%)</td>
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</tbody>
</table>
Safety Measures: Blood Pressure and Weight

- Transdermal nicotine was well tolerated in an older non-smoking population.
- Side-effect rates similar between nicotine and placebo.
- No serious events judged secondary to nicotine.
- No adverse effects on vital signs from nicotine other than decrease in weight.
Nicotine MCI Pilot Study: Improvement in Attention and Memory by 3 Months

Attention

Memory

Continuous Performance Task: Hit Rate SE. \( p = 0.0003 \) for Nicotine Treatment

Newhouse, et al 2012

Significant Improvement seen in attention, verbal episodic memory and psychomotor speed, trends for clinical rating improvement. **Sustained to 6 months.**
APOE Genotype Modulates Nicotine Effect: Greater Effect in APOE4+/+

Power of Attention
Nicotine p=0.0812  Nicotine*APOE p=0.0475

Digit Vigilance Task - Speed of Detections
Nicotine p=0.0505  Nicotine*APOE p=0.0144

APOE Genotype Modulates Nicotine Effect: Greater Effect in APOE4+/+
Chronic Nicotine Upregulates and Sensitizes Brain Nicotinic Receptors

Exposure to nicotine produces *stronger activation at upregulated receptors* because upregulated nAChRs are both more numerous and more sensitive.

Miwa et al, 2014
The MIND Trial

- Long-Term Nicotine-MCI Trial
  - Nicotine vs Placebo for 2 Years
  - Cognition and Function as primary endpoints.
  - Examine nicotine treatment effects on biomarker change over time (MRI, CSF).
  - Explore genetic and metabolic correlates.

- National Principal Investigator:
  Paul Newhouse, M.D., Vanderbilt University

- 32+ US sites

- Coordinating Center: Alzheimer’s Therapeutic Research Institute - University of Southern California

- Web Site: MINDStudy.org
MIND Study Overview

- Test whether transdermal nicotine enhances cognitive performance and clinical outcome in patients with MCI over a sustained period of time.
- Non-smoking adults diagnosed with MCI ages 55+.
- Study partner required.
- 2 year length of double-blind treatment.
- Testing treatment effects on cognitive performance, clinical assessment and biomarkers (MRI, CSF).
**MIND: Multi-Modal Measures of Treatment Effects and Biomarkers**

- **Cognitive Assessment:** Connors CPT; CogState computerized battery); Story recall.

- **Clinical Outcome Measures:**
  - CGIC-MCI; Clinical Dementia Rating (CDR) Sum of Boxes; Older Adult Self Report and Checklist (OASR/OABCL).

- **Biomarkers of Disease Progression:**
  - Structural MRI (e.g. hippocampal volume; GM density using ADNI-3 protocol, etc); fMRI (working memory and resting state) CSF aβ42; tau.

- **Genetics:** DNA to be banked; APOE, CYP2A6 phenotype/genotype

- **Safety:** Vital signs; Adverse events; Nutritional assessments

- **Resting State fMRI:** Planned examination of canonical brain networks for changes following drug treatment: *Default mode; Executive Control; Dorsal Attention*

- **Task-based fMRI:** N-Back Working Memory Task
  - Drug-Induced Modulation of Task-related activity
Nicotinic Stimulation of Cognitive Decline in Down Syndrome

PET scan of amyloid and tau protein (tangles) in control, young and elderly patients with DS, and Alzheimer’s Disease (Small et al 2011)

Cholinergic markers are reduced in DS
Adults with Down Syndrome: Pilot Safety and Efficacy trial of Daily Transdermal Nicotine Treatment

Event-Related Potential Testing (Event-Related Potentials: memory and attention)

*Compare to baseline, and evaluate for signs of improvement*

Late changes in cortical trace amplitude reflect altered memory/learning ability in older DS.

Incidental Memory Task for DS

- 50 novel real-life images
  - 10 randomly selected to be repeated
- 10 attention probes
- 1500ms duration
- 1100-1300ms ISI
- 7 min total test time

ERPs to novel and repeated stimuli in adults with DS.

Key & Dykens (2014) *Neurobiology of Aging*
Chronic nicotine improves cognitive functioning in lower performing older adults with DS

N = 5
Higher Functioning DS: *Worsening* of Performance/ERP after Nicotine: Sensitivity to Baseline Performance

Newhouse et al, 2004
Nicotinic Augmentation of Antidepressant Treatment in Late Life Depression (LLD)

• The co-occurrence of cognitive deficits in LLD is characterized by significant disability; poor antidepressant response: increased risk of depression relapse.
• The lack of treatments that improve cognitive deficits in depression is a deficiency in current therapeutics.
• Hypothesis is that in LLD, transdermal nicotine will safely improve depression by:
  – increasing activity in cognitive control regions and decreasing activity in Default Mode Network (DMN) regions.
  – Result in decreased attentional bias to and reactivity to negative stimuli.
Nicotinic Modulation of Resting State Network Activity in Depression

- nAChR agonists appear to influence key intrinsic networks.
- Network effects influence cognitive performance, core depressive behaviors (negativity bias, rumination)
- The ability to modulate mood may depend on these cognitive factors.

Gandelman, Newhouse, & Taylor, 2017
Transdermal nicotine effects on depression severity \textsuperscript{a}

\textsuperscript{a} Data Points show mean MADRS and 95% CI over time
MADRS = Montgomery-Asberg Depression Rating Scale

Gandelman et al, J Clin Psych (in press)
Nicotinic Treatment of Late-Life Depression: Evidence for target engagement

ERP Go/NoGo Task: Enhanced CNV and post stimulus positivity amplitude (C3)

qEEG: Auditory Oddball Task. Following nicotine treatment, reduced theta power and increased beta activity following target

Gandelman et al, under review
The cholinergic hypothesis is evolving from a primary focus on memory toward expanded cognitive functions modulated by regionally more complex and interactive brain networks.

Bohnen et al, 2018
Model of Nicotinic Enhancement of Cognitive Functioning: *Resource Enhancement*

Particularly Relevant to Syndromes that Resemble Accelerated Aging
Nicotinic Stimulation Improves Low Baseline Cognitive Performance

Loss of Dynamic Range in Cholinergic Augmentation of Cognitive Functioning with Progressive Neurodegeneration

Newhouse et al, 2004

Dumas and Newhouse 2011
Cognitive Impairment that is Secondary to the Combination of a Brain Disorder and Aging: Target for Nicotinic Stimulation

Disorders which exhibit deficits that exaggerate normal aging changes in attentional/executive/memory functioning may be candidates for nicotinic augmentation.

MCI, Down Syndrome, Late-Life Depression, ADHD, HIV-HAND, Post-chemotherapy (“chemobrain”), Post-Delirium Cognitive Impairment, etc…

Such treatment directed at symptomatic cognitive improvement may be orthogonal to diagnosis, thus cutting across disease categories, especially when combined with aging.

Collaborators

MIND:

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THE WILLIAM K. WARREN FOUNDATION

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