A crossover atropine titration study in the Olfactory Stress Test for the diagnosis of Alzheimer’s Disease.

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Statement of Originality

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**Unless an Embargo has been approved for a determined period.
Suddenly you were gone, from the all the lives you left your mark upon

Neal Peart

In Memoriam

This thesis is dedicated to the memory of very important men who experienced dementia—some of the Alzheimer’s type; some not—and to their beloved families.

Salvador “Papapa” Levy Z”L
Benjamin “el Zeide” Mankevich Z”L
“Grandpa” Harry Bricker Z”L

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Last but not least, not by a long shot

How is it that the chorus to that song you like go? If you’re lost you can look, and you will find me?... If you fall I will catch you, I’ll be waiting, time after time. Yeah, that’s my wife Joanne Benhamu for me. She’s pulled me up and pushed me forward every single time. She’s been strong for both of us during all these years of me trying to get it together. I’m lucky. I love you beyond measure. Your turn now, Ms. Shafer! It’s my turn to catch you.

...I catch a break, then a punch to the head; I smile big with a toothless grin (P.J.)
Table of Contents

Abstract.................................................................................................................................................. 6
Literature Review.................................................................................................................................... 9
Manuscript............................................................................................................................................... 26
Abstract............................................................................................................................................... 27
Background.......................................................................................................................................... 28
Study aims.............................................................................................................................................. 29
Olfactory changes occur in Alzheimer’s Disease and may precede obvious cognitive impairment .................. 31
Pathological changes of AD affect cholinergic neurotransmission and are related to olfactory decline .......... 32
  Olfaction and cholinergic neurotransmission....................................................................................... 32
  AD pathology affecting cholinergic activity and impact on behaviour ............................................ 33
  Association between genetic predisposition and pathology of AD .................................................... 34
The Olfactory Stress Test (OST): Rationale and Results....................................................................... 36
Methods ................................................................................................................................................. 37
  Sample and Participant Selection....................................................................................................... 37
  Inclusion and exclusion criteria........................................................................................................... 38
  Assessment and Measures.................................................................................................................. 39
    Audio Recorded Cognitive Screen (ARCS)........................................................................................ 39
    Genotyping...................................................................................................................................... 40
  University of Pennsylvania Smell Identification Test (UPSIT)........................................................... 40
  Atropine Solution.............................................................................................................................. 41
Experimental procedures and study design............................................................................................ 41
  Participant induction............................................................................................................................ 42
  Olfactory Stress Test (OST)................................................................................................................ 42
  Statistical analysis.............................................................................................................................. 43
Results..................................................................................................................................................... 44
  Results according to groups divided by neuropsychological ability ............................................... 45
  Results according to Groups divided by Genotype............................................................................ 46
Discussion............................................................................................................................................... 47
Conclusion............................................................................................................................................. 51
Abbreviations....................................................................................................................................... 51
Competing interests .............................................................................................................................. 51
Abstract

Scope: The Olfactory Stress Test (OST) is a potentially new method to screen for Alzheimer’s disease (AD) at its prodromal stage. There is pressure to find methods of early AD detection in preparation for a time when disease altering drugs become available. Presently, the use of early detection could assist prompt intervention, which could allow patients to start taking acetylcholinesterase inhibitors early for maximum effect. Early intervention has also been shown to improve the quality of life of patients and their caregivers. The OST relies on the cholinergic hypothesis, which posits that AD is driven by a decline of cholinergic activity in the brain. It is understood that cholinergic decline happens before cognitive deficits associated with AD appear. Cholinergic activity in the olfactory bulbs (OBs) influences the relay of environmental cues to the olfactory processing centre of the brain. As such, olfaction also declines during AD even before the emergence of cognitive problems: a fact that is yet to be harnessed in clinical practice for early disease detection. The OST uses an atropine anticholinergic solution intranasally to exacerbate the already compromised cholinergic activity in the OB. This effect is measured by subtracting the score of the University of Pennsylvania Smell Identification Test (UPSIT) administered before the atropine intake from that of an UPSIT administered after the atropine. This difference yields the atropine effect (AE), which is hypothesized to reflect the presence of Alzheimer’s disease pathology in the OB. Healthy individuals should yield a positive and negligible AE reading. A previous OST study has shown promise for this technique. This study was part of an effort to further develop and refine the OST.

Purpose: The aim of this study was to titrate atropine doses. Researchers looked for a dose lower than the 1 mg concentration dose currently used in OST research. The
purpose of this titration study was to determine if a lower atropine dose would elicit a meaningful AE while reducing the risk of potential side effects.

Methodology: Ten participants (six women) over the age of 65 volunteered for this study. Three of the participants responded to a recruitment drive aimed at organizations serving seniors in the Lake Macquarie Municipality. The remainder of the participants had volunteered in previous OST studies and agreed to partake in this titration study after being contacted by a research trial coordinator assisting with the administrative aspects of the study. The methodology followed a repeated measures cross-over design. The researchers administered three concentration doses of atropine to each study participant: 0.1 mg, 0.5 mg and 1 mg. Doses were administered one week apart from each other. During the first session, researchers took a medical history of the participants and administered the Audio Recorded Cognitive Screen (ARCS). ARCS composite scores were used to divide participants between MCI/AD and Control (i.e. those with normal cognitive function). Participants were screened for the presence of the Apolipoprotein ε4 allele, which has been associated with increased risk of developing Alzheimer’s. Genotyping was used to separate participants between Risk and No Risk groups.

Results: Two linear mixed models were conducted: The first linear mixed model looked at the data according to participants divided by ARCS performance and the second one according to group genotype risk. Both linear mixed models explored the fixed effects of research group (i.e. neuropsychological performance and genotype risk respectively), atropine dose and their interaction. The linear mixed model conducted on ARCS-score groups yielded no significant effects. The linear mixed model conducted on genotype risk groups yielded a significant effect for genotype risk for the .5mg atropine dose at $\alpha<.05$, $F=15.634$, $p=.004$. The No Risk group yielded an AE that was positive, $M=.5,$
95% CI [-1.83, 2.83], whereas the Risk group yielded a negative AE, $M=-4.67$, 95% CI [-7.96, -1.38] at the .5 dose. These results were consistent with OST theory.

Conclusions and implications: Although some significant effects were found, the results need to be addressed with a degree of caution considering the small sample size. Other biases may have been introduced by the crossover design. Further research with larger samples is in order to find a lower, effective dose of atropine in the OST.