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PRINCIPAL INVESTIGATOR: Dr. Davangere Devanand

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14. ABSTRACT Background. A large proportion of patients with amnesic mild cognitive impairment (MCI) convert to Alzheimer's disease (AD) and hence acetylcholinesterase inhibitors (AChEI) are commonly prescribed in patients with MCI though it is not FDA approved for this condition. Therefore, predicting which MCI patients are likely to improve cognitively with AChEI treatment is important. Hypotheses. 1. The acute decrease in UPSIT (Odor identification test) scores from pre- to post- atropine nasal spray challenge conducted at baseline (0 weeks) will be associated with cognitive improvement (SRT total recall and modified ADAS-cog) from baseline to 26 weeks and 52 weeks of donepezil treatment. 2. Increase in UPSIT scores from baseline to 8 weeks of donepezil treatment will be associated with cognitive improvement from baseline to 26 and 52 weeks. Exploratory Hypothesis. The acute atropine-induced decrease in UPSIT scores, and increase in UPSIT scores from baseline to 8 weeks, will be associated with a decreased likelihood of conversion to dementia at 52 weeks. Study Design. In this proof of concept study, 60 patients with mild cognitive impairment will be treated openly with donepezil 5 to 10 mg per day and followed for 52 weeks (one year), with an atropine challenge test also conducted at baseline.					
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INTRODUCTION: Individuals with cognitive deficits, whether due to traumatic brain injury or due to mild cognitive impairment, may improve with donepezil treatment. Olfactory identification deficits may be an early test that can identify who in the high-risk population is most likely to develop dementia and therefore identifies patients for early interventions. Based on the study results, the presence of olfactory identification deficits can be used to decide if the patient should receive treatment with a cholinesterase inhibitor like donepezil.

BODY: 168 patients have been screened for this protocol. 41 patients have been recruited. 4 patients never began the study, 5 patients chose to dropout of the study, and 32 patients have completed the study. No patients remain active in the protocol. Of the 32 completers, 15 were female and 17 were male. The mean age of the patients was 71.15 years, standard deviation 9.90.

All completers have been given baseline pre and post atropine spray UPSITs, have completed all procedures according to the protocol schedule, and have been treated with either 5mg or 10mg Donepezil daily. Of the completers, 10 patients could not tolerate donepezil 5 mg daily. For clinical reasons, they were started on a comparable cholinesterase inhibitor, galantamine or rivastigmine, and were followed at the scheduled time-points as per the intent-to-treat principle employed in this study. The data obtained will be analyzed in two ways: in primary analyses we will count donepezil dropouts with subsequent time-point assessments handled as planned originally under the intent-to-treat principle, and in secondary analyses we will combine the data in patients who receive donepezil or galantamine or rivastigmine since they are all cholinesterase inhibitors with very similar effects on cognition and function (and we will include all assessments under the intent-to-treat principle). This change was approved by the NYSPI/Columbia local IRB and also approved by the DoD regulatory authorities.

There have been two adverse events to date, neither of which was rated as being related to study medication.

1. A patient was admitted to the hospital for 4 weeks for neglecting to take his psychiatric medications and alcohol abuse. He was released, now has a well-defined psychosocial support team involved in his care, and has completed our study.
2. A patient began seeking treatment for urinary symptoms and was diagnosed with cancer in his left kidney with accompanying bladder involvement. He received focused beam radiation, and reported at his most recent clinic visit that he felt fine and considered himself lucky that the cancer was caught and treated as efficiently as it was. He has since completed our study.

Intranasal Atropine has been administered to 37 subjects. For the last 29 subjects, we used the “squirt system”, developed by Scheibe et al (2008). The squirt system includes a 2 cm sterile plastic tube attached to a one cc syringe. The syringe is filled with 0.1 cc of atropine and then the tube is placed in the nasal cavity parallel to the nasal septum, and directed at the nasal cleft (back and up towards the cribriform plate). The atropine is then squirted up towards the superior turbinate bone in the nose. This is immediately followed by the standard 1 minute Mecca position, 45 minute delay, and repeat UPSIT test, as before. The squirt system produced more consistent results. In September 2013, we submitted the “Atropine Nasal Spray for Olfactory Challenge in Humans” to the Militarily-Relevant, Peer Reviewed Alzheimer’s Disease Program’s (MRPRA) “Product Database”.

From a data analytic standpoint, we will first include all subjects in evaluating the change in UPSIT from pre- to post-atropine spray as a predictor of donepezil treatment response, and then separately assess the impact of the first 8 subjects where different techniques were used as noted above. We will include and then exclude the subset of the first 8 patients in statistical analyses and then assess if the results change. Of note, the atropine challenge-induced change in UPSIT scores represents the first of the two main hypotheses; the second hypothesis pertaining to change in UPSIT scores from baseline to 8 weeks as a predictor of longer-term donepezil response is unaffected by the change in the atropine spray challenge procedure.

KEY RESEARCH ACCOMPLISHMENTS: No presentations or publications to date from this study; results of data analyses from the finalized database are described below.

REPORTABLE OUTCOMES:

Summary of findings:

Hypotheses were assessed using linear mixed effects models with a random intercept for each subject. In these models the response was change in score (either ADAS-cog or SRT total recall) from baseline to either 26 or 52 weeks. All models included the covariates of time and change in UPSIT (either acute change after atropine challenge or over 8 weeks). We also considered models adjusting for age, education, gender and APOE e4 status. A level of 0.05 was used as the threshold for significance.

Before testing the specified hypotheses, we examined whether there was an interaction between week of evaluation for the main outcomes (26 and 52 weeks) and the two predictor variables: change in UPSIT scores from pre- to post-atropine nasal spray, and the change in UPSIT scores from 0 to 8 weeks. These interactions were not significant, supporting direct testing of the study hypotheses.

The atropine nasal spray procedure was initiated in the first 8 subjects and then refined by using a different spray nozzle that was longer and more flexible based on the ENT literature; this has been described in our DoD progress reports. The findings were similar whether these 8 subjects were included or excluded; we now report the findings for all available subjects. Also, the results were similar whether or not we separated those few patients who received galantamine or rivastigmine instead of donepezil, and we report on the total sample of patients who received cholinesterase inhibitors.

Demographics

There were 37 subjects with complete baseline data. All subjects were diagnosed with mild cognitive impairment as per inclusion/exclusion criteria. At baseline, mean age was 70.35 (SD 9.76) years, 54.05 percent were male, and 38.9% were positive for the apolipoprotein E e4 allele (heterozygous or homozygous). Mean baseline UPSIT score was 26.81 (SD 7.43).

Hypothesis 1.

The acute decrease in UPSIT (40-item odor identification test) scores from pre- to post- atropine nasal spray challenge conducted at baseline (0 weeks) will be associated with cognitive improvement (SRT total recall and modified ADAS-cog) from baseline to 26 weeks and 52 weeks of donepezil treatment.

Mean change in UPSIT score for post-pre atropine nasal spray was -0.32, SD 3.84. Analyses included all patients with at least one follow-up assessment (n=32).

The acute decrease in UPSIT score was not associated with change in **ADAS-cog** from baseline to 26 weeks and 52 weeks on donepezil treatment ($F=0.0934$, $p=0.7757$), and remained non-significant ($F=0.0368$, $p=0.8642$) after adjusting for age, education, sex, APOE e4 status, and time. In this analysis, APOE e4 allele positive status was associated with improvement in ADAS-Cog scores (decrease in ADAS-Cog scores; $t=-2.06$, $p < 0.05$).

The acute decrease in UPSIT score was associated with change in **SRT total recall** from baseline to 26 weeks and 52 weeks on donepezil ($F=5.41$, $p < 0.03$) and remained significant after adjusting for age, education, sex, APOE e4 status, and time ($F=4.54$, $p < 0.05$). APOE e4 status was not a significant covariate in these analyses. More specifically, our model suggests that a one-point decrease in change in UPSIT score corresponds to a 0.58 increase in change in **SRT total recall** on average ($p = 0.0413$), adjusting for age, education, sex, APOE4 status, and time.

Hypothesis 2.

Increase in UPSIT scores from baseline to 8 weeks of donepezil treatment will be associated with cognitive improvement (ADAS-Cog and SRT total recall) from baseline to 26 and 52 weeks.

Mean change in UPSIT score from baseline (week 0) to week 8 was -0.35, (SD 4.38).

Change in outcome measures over the 52-week study:

Analysis Variable : ADAS_cog							
Week	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
0	36	10.33	4.07	0.68	4.33	9.83	21.00
8	35	9.81	3.76	0.64	3.00	10.33	18.00
26	32	8.65	3.64	0.64	3.67	7.83	18.33
52	32	9.84	4.34	0.77	2.00	9.33	19.00

Analysis Variable : SRT_Total Recall							
Week	N	Mean	Std Dev	Std Error	Minimum	Median	Maximum
0	36	33.61	8.15	1.36	16.00	34.00	48.00
8	35	36.23	9.27	1.57	19.00	37.00	56.00
26	32	36.81	9.22	1.63	20.00	36.00	55.00
52	32	37.13	10.59	1.87	18.00	35.50	57.00

The change in UPSIT score from 0 to 8 weeks (post-pre) was not associated with change in **ADAS-Cog** from baseline to 26 weeks and 52 weeks on donepezil without covariate adjustment, but there was a trend-level effect ($t= -1.74$, $p=0.092$) after adjusting for age, education, sex, APOE4 status, and time. More specifically, our model suggests that a one-point increase in

change in UPSIT score from baseline to week 8 corresponds to a 0.22 decrease in change in **ADAS-Cog** on average ($p = 0.092$), adjusting for age, education, sex, APOE4 status, and time.

The change in UPSIT score from 0 to 8 weeks (post-pre) was not associated with change in SRT total recall score from baseline to 26 weeks and 52 weeks, both without and with covariate adjustment.

CONCLUSIONS

The change in UPSIT from pre to post atropine challenge was associated with increased SRT total recall but not with the ADAS-cog. The results with SRT total recall support the notion that lower UPSIT performance after atropine challenge is caused by decreased cholinergic transmission and that it can be predictive of longer term response to cholinesterase inhibitors like donepezil. The effect size was not large, and a larger sample with the addition of other neuropsychological tests is needed to confirm the findings before it can be recommended for widespread clinical application to determine which patients should or should not receive cholinesterase inhibitor treatment.

For hypothesis 2, there was the suggestion that the increase in UPSIT scores with 8 weeks of donepezil treatment was associated with improvement in ADAS-Cog test performance, but the results were at trend-level and did not reach statistical significance. Questions have been raised about the sensitivity of the ADAS-Cog to milder forms of cognitive impairment that do not meet criteria for dementia (Podhorna et al, 2016), and in our study of patients with mild cognitive impairment (MCI) the impairment on the ADAS-Cog was minimal at baseline and throughout the study. The finding of cognitive improvement on donepezil being greater in patients with the APOE e4 allele are consistent with the earlier reported findings in the large-scale donepezil-vitamin E study in MCI (Petersen et al, 2005) and may be worth investigating systematically in larger samples with odor identification testing.

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APPENDICES:

None.