The impact of Anticholinergic Burden in Alzheimer's Dementia-The Laser-AD study

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Authors
Dr Chris Fox Mmedsci
University of East Anglia Norwich UK
Professor Gill Livingston MD
University College London UK
Mr Ian D Maidment BPharm
Centre for Health Service Studies University of Kent UK
Kent and Medway NHS and Social Care Partnership Trust UK
Professor Simon Coulton PhD
Centre for Health Service Studies University of Kent UK
Dr David Smithard MD
East Kent NHS Community services + Kent Comprehensive Research Network UK
Assistant Professor Malaz Boustani MD
Indiana University Center for Aging Research Indiana University School of Medicine USA
Professor Cornelius Katona MD
University College London UK

Corresponding Author:
Dr Chris Fox
Reader in Psychiatry/Hon Consultant Psychiatrist/
Research Director East Anglia DeNDRoN
School of Medicine, Health Policy and Practice
University of East Anglia
Earlham Road
Norwich,UK
NR4 7TJ
Telephone 01-603-223583
Fax 01-603 -593233
Chris.Fox@uea.ac.uk

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Abstract

Objective

To examine the effect of medications with anticholinergic effects on cognitive impairment and deterioration in a cohort of people with Alzheimer's Dementia (AD).

Methods

Cognitive function was measured at baseline and at 6 and 18 month follow-up using the Mini-Mental State Exam (MMSE), the Severe Impairment Battery (SIB) and the Alzheimer's Disease Assessment Battery, Cognitive subsection (ADAS-COG) in a cohort study of 224 participants with Alzheimer's Dementia (AD). Baseline anticholinergic Burden Score (ABS) was measured using the Anticholinergic Burden Scale and included all prescribed and over the counter medication.

Results

The average number of medications taken was 3.6 (SD 2.4) and the mean anticholinergic load was 1.1 (SD 1.4, range 0-7). The total number of drugs taken and anticholinergic load correlated (rho=0.44 $p<0.01$). There were no differences in MMSE and other cognitive functioning at either 6 or 18 months after adjusting for baseline cognitive function, age, gender and use of cholinesterase inhibitors between those with, and those without high anticholinergenic load.

Conclusions

Medications with anticholinergic effect in patients with AD were not found to effect deterioration in cognition over the subsequent 18 months. Our study did not support a continuing effect of these medications on people with AD who are established on them.

Introduction

There is increasing evidence that medications with anticholinergic effects may adversely affect cognitive function [1, 2]. Older people are particularly sensitive to anticholinergic effects due to the significant age-related decrease in cholinergic neurons or receptors in the brain, the reduction in hepatic and renal clearance of medications, and the increase in blood-brain barrier permeability particularly in acute physical illness [3]. Older people are also at relatively high risk of being exposed to medications with anticholinergic effects, due to their high medical morbidity, their frequent use of prescribed and over-the-counter medications; those that take such medication are more likely to be cognitively impaired than those who do not [4]. In the US it is estimated that 20-50% of patients with dementia, take at least one medication with some anticholinergic activities [5,6,7].

Cholinergic mechanisms have been implicated in the aetiology of delirium, to which older people are also vulnerable [8]. People with Alzheimer's Disease (AD) may be at particular risk of cognitive deterioration secondary to medications with anticholinergic effects because of their marked reduction in the functioning of their central cholinergic pathways [9].

The aim of this study was to examine whether cholinergic burden was associated with the magnitude of current cognitive impairment or predicted the rate of future cognitive deterioration in a cohort of people with AD participating in a naturalistic follow-up study.

METHODS

The study is part of a larger longitudinal cohort study of 224 participants with AD, the

London and South East Region AD (LASER-AD) study[10]. People with AD and their carers were approached through a variety of sources: their local community mental health team, dementia specialist nurses, the voluntary sector (including the Alzheimer's Society), memory clinics, nursing and residential homes, day hospitals and inpatient units. Some of the participants had not received a diagnosis of AD, but the doctor in the research team screened and confirmed the diagnosis in all the participants. The participants were prospectively recruited purposively in order to be a sample of people with AD similar to that in the general population in terms of severity of cognitive impairment, gender and living situation [11].

The inclusion criteria were a standardised diagnosis of dementia [12] and fulfillment of criteria for possible or probable AD[13], being aged over 55 years, living in either North London or Essex and being in contact with a family or statutory carer for at least four hours a week. The interviews were conducted by trained, experienced health professionals and comprised socio-demographic details, a medical and psychiatric history and physical examination. Follow-up interviews were undertaken at 6 and 18 months. Cognitive function was measured at baseline and at follow-up using the following: (1) Mini-Mental State Exam (MMSE) [14] Potential score ranges from 0-30. (2) The Severe Impairment Battery (SIB) [15] The SIB assesses the cognitive abilities of more impaired patients with dementia. Potential scores range from 0 to 100 [16,17] and (3) the Alzheimer's Disease Assessment Battery, Cognitive subsection (ADAS-COG)[18]. The range is 0–75; higher scores indicate greater dysfunction.

The researcher documented all the prescribed and over the counter drugs that each patient was taking at baseline.

For the purposes of this study, each LASER-AD participant's 'anticholinergic burden' was calculated using the Anticholinergic Burden Scale (ABS) which we had previously developed [19,20,21]. The scale was developed through a systematic review of the literature to identify drugs with documented anticholinergic activity. Content validity was tested by presenting the list to an expert interdisciplinary panel that included geriatricians, pharmacists, old age psychiatrists, general physicians, specialist geriatric nurses, and aging brain researchers. Using their clinical and basic science expertise as well as the documentation provided, a consensus approach was used to classify the potential anticholinergic effects of individual drugs into four groups (none = 0; mild = 1; moderate = 2; severe = 3). An individual's 'anticholinergic burden' (ABS) can then be calculated by summing the scores for all the drugs that patient is taking. Its predictive validity of cognitive decline has been shown in two large samples of community-dwelling older people[21,22,23]. The ABS captures individual medication therefore to facilitate medication coding three investigators (CF,IM, DS) reviewed all medication content to code medications not covered, such as mixed formulations, Finally, three authors (CF, CK, IM) reviewed the individual patient medication lists collected at baseline to calculate the total ABS in each patient. Any disagreement was resolved by discussion until a consensus was obtained.

Analysis

We report descriptive statistics and as appropriate parametric or non-parametric correlation coefficients of ABS load with cognitive outcome and possible confounders. To correct for multiple testing, we considered an alpha value of $p < 0.01$

as significant and to explore the impact of ABS load on cognition at 6 and 18 months, we conducted an analysis of covariance with a dichotomous fixed factor, ABS > 0 and ABS = 0, with the ADAS-COG, MMSE and SIB at 6 and 18 months as the dependent variables, controlling for confounding covariates; baseline measures of cognition, age, gender and whether patients where receiving a cholinesterase inhibitor. Where necessary to meet the assumptions of analysis of covariance, outcomes were transformed with the results being transformed back for ease of interpretation.

Power calculation

Our sample size was sufficient to detect a clinically significant correlation (conventionally taken as 0.4 or greater) at the 0.001% level (http://department.obg.cuhk.edu.hk/index.asp?scr=1280).

Results

We interviewed 224 people (160 women; 71.4%) with AD at baseline. 151 were living at home and the remainder in institutional care. Their mean age was 81.0 years (SD 7.4 [range 55-98]). At 18 months, 167 (74.6%) people completed follow-up. A total of 48 (21.4%) had died. Eight (3.6%) refused to take part. One (0.4%) had moved too far away to be interviewed. Participants who died were older (mean: 84.4 [SD 6.5] vs 80.20 [SD 7.5] $p < 0.001$) and more cognitively impaired on MMSE (mean: 11.0 [SD 8.3] vs 15.68, [SD 7.4] $p < 0.001$), and more likely to be living in 24-hour care accommodation (24 [50.0%] vs 48 [28.7%], $p < 0.01$). Participants, who refused were not significantly different demographically from the rest of the population. The description of the baseline population is shown in table 1. At baseline those with a

greater ABS has a lower level of cognition as measured by the SIB and MMSE.

The average number of medications was 3.6 (SD 2.4) and the mean anticholinergic load was 1.1 (SD 1.4) with a range of 0-7. At baseline 47% of participants were on cholinesterase inhibitors; at 18 months this had risen to 56%. There was no effect of use of cholinesterase inhibitors on the results.

The results confirmed the expected correlation between total number of drugs taken and anticholinergic load (rho=0.44 $p<0.01$). There were no significant correlations between changes in cognitive score and the total number of medications taken (Table 2).

There was no significant correlation between ABS score and cognition using any of the three measures (ADAS-COG, MMSE and SIB) at baseline, 6 months or 18 months. ABS baseline scores were not normally distributed, with 101 participants having an ABS score of 0, 58 participants a score of 1 and 63 participants a score > 1. In order to have large and similar numbers of people in both groups, we compared baseline cognitive scores between participants with ABS scores of 0 and those with ABS scores of 1 or more. For participants with information available at both time-points, we also compared cognitive scores at 6 and 18 months, adjusting for baseline cognitive scores, use of cholinesterase inhibitors, age and gender, between the groups with baseline ABS score of 0 and the group with a score of ≥ 1 . These results are summarised in Table 3. There was no significant difference between the groups on any of the cognitive measures.

There was no correlation between baseline anticholinergic load (as a continuous variable) and change in MMSE (rho=0.03 NS), change in ADAS-COG (rho=0.09 NS) or change in SIB (rho=0.08 NS) at 18 months.

Discussion

This is the largest study of an Alzheimer naturalistic cohort to consider the effect of cholinergic burden on cognition of people with AD. Its strengths include that it had more than adequate power and used three different instruments to measure cognition to ensure there was no ceiling or floor limitation in measurement and to traingulate the findings. There was no effect on cognition, either at baseline or 18 months later. The commonest group of medications in this sample with anticholinergic effects were psychotropics. The failure to show any effect contrasts with other studies which have looked at non-dementia samples where an effect has been found using the same assessment tool [20,21] . In a previous paper from the LASER study, we have however reported the absence of correlation between exposure to (and dosage of) atypical psychotropic medication and cognitive decline when neuropsychiatric symptoms were taken into account [24].

The lack of an effect of ABS in this study (in contrast to the positive findings in a smaller but similar study[25]) may be because of the decreased sensitivity of patients with more advanced cognitive impairment or because those on established anticholinergic medication do not deteriorate on cognition more quickly. This is supported by the group with a clinically meaningful ABS at baseline having lower cognition sores as measured by the MMSE and SIB at baseline. Alternatively, therapeutically the result could be interpreted as suggesting that medications with anticholinergic effects may not be as damaging to cognition as first thought in established dementia..

There are a number of limitations of this study which may also have contributed to the negative results. The average anticholinergic load score and number of medications patients were taking were low. However, this and the number of medications with anticholinergic effects were in line with other studies in different population which showed an association[20,21]. The duration of follow up of 18 months may be seen as a limitation, but this is long enough to see a clinically relevant effect in this population. We only examined baseline medication and the effect of compliance was not measured. We may have missed the stage of critical importance for medications with anticholinergic effect beyond which damage to the cholinergic system had already occurred and may have passed a critical threshold. The ABS scale may lack sensitivity to detect an association. Additionally about half the people in our study were taking cholinesterase inhibitors which may have masked the cognitive effects of co-prescribed medications with anticholinergic effects. However when this was analyzed there was no effect but this may have been limited by the small sample size. We did not have complete data on dosages of anticholinergic drugs and the duration that individuals were exposed to them.

The ABS Scale has recently been validated as a predictor of cognitive impairment in two large samples of community-dwelling older people of patients without dementia [20,21,22]. Ideally it should also be validated against a biomarker 'gold standard'. Reviews of the relevant literature concluded that radio-receptor assay may provide a reliable, reproducible and potent predictor of the impact of these medications on cognition[26,27] . Such an approach would need to consider dose of medication and the effect of more than one drug with anticholinergic effects. Radio-ligand assays rely on

serum samples and use rodent tissue. However this may not represent in vivo effects as the blood brain barrier permeability can alter and the muscarinic receptor blockade on serum may not be representative of brain tissue effects[19,20,28,29]. This approach should be incorporated into a future study in order to validate non-laboratory assessment tools.

The scale we used is broad and covers all representative medication; however there may be particular types of medication with anticholinergic effects which have a particularly potent effect. Such specific effects might have been lost with the present scale. A further area of further development of the scale is that it does not take into account the effect of dose of medication, for example, a patient prescribed 5mg of procyclidine daily will have the same burden score as a patient prescribed 30mg of procyclidine daily. The tool should be further developed to take into account dosage.

We conclude that, in this study of people with Alzheimer's disease, that taking possibly a low dose of one medication with a low degree of anticholinergic activity (an ABS score of 1) does not predict more impaired cognition or a more rapid cognitive decline over the next 6 or 18 months. Furthers studies are needed which include people who are cognitively intact as well as those with dementia and use an instrument which is validated against a biomarker.

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Table 1: Baseline description of the sample

	ABS = 0	ABS>=1	p-value
Mean number of drugs (SE)	2.53 (0.18)	4.58 (0.21)	<0.001
% Male	32	26	0.22
Mean age (SE)	80.48 (0.69)	81.47 (0.71)	0.32
Mean MMSE Score (SE)	16.20 (0.81)	13.50 (0.75)	0.01
Mean ADASCOG (SE)	34.42 (1.92)	40.04 (1.91)	0.04
Mean SIBTOT (SE)	82.52 (2.70)	30.94 (2.80)	0.07
% Taking CHEI	59	47	0.06

Table 2: Correlations between change in cognitive score and total number of medications

	Pearson Correlation with total number of drugs taken	Sig (2-tailed)	N
Change in MMSE BL to 6months	0.14	0.054	163
Change in MMSE BL to 18 months	0.06	0.47	163
Change in SIB BL to 6mths	0.04	0.61	195
Change in SIB BL to 18 months	0.01	0.94	152
Change in ADAS-COG BL to 6month	0.06	0.36	224
Change in ADAS-COG BL to 18 months	0.03	0.67	156

Table 3: Baseline, month 6 and 18 and adjusted mean differences for cognitive measures categorized by ABS score 0 or 1 or more.

Cognitive Measure	Baseline mean (95% CI n)	Month 6 mean (95% CI n)	Month 6 Mean difference (95% CI)	Month 6 p-value	Month 18 mean (95% CI n)	Month 18 Mean difference (95% CI)
ADAS-COG ABS=0	29.67 (26.58; 33.12) n=224	31.37 (29.66; 33.18) n=156	-1.59 (-1.14;1.03)	0.22	33.92 (31.50; 36.56) n=156	-1.49 (-1.96; 1.06)
ABS=/>1	34.47 (31.19; 38.47)	32.96 (31.25; 34.78)			35.41 (32.88; 38.17)	
MMSE ABS =/> 0	16.20 (14.60;17.80) n=224	14.52 (13.79; 15.24) n=163	0.53 (-0.47;1.53)	0.26	13.08 (11.98; 14.16) n=163	0.69 (-0.84; 2.21)
ABS =/> 1	13.50 (12.02; 14.99)	13.99 (13.32; 14.67)			12.39 (11.34; 13.44)	
SIB ABS = 0	82.53 (77.16; 87.89) n=224	77.68 (74.75; 80.62) n=195	1.75 (-2.28; 5.77)	0.39	74.75 (70.11; 79.38) n=152	6.23 (-0.26; 12.73
ABS =/> 1	75.41 (69.86; 80.96)	75.94 (73.22; 78.65)			68.51 (64.02; 73.00)	

Covariates included in the model are baseline values, age and gender