Alzheimer’s disease (AD) is the most common form of dementia in the UK. There is currently no cure for dementia or AD, but there are treatments which can modestly improve symptoms - including cholinesterase inhibitors (such as donepezil) and glutamate antagonists (such as memantine). However prior to DOMINO-AD, there was limited evidence to guide treatment decisions as AD patients advanced beyond the mild to moderate severity stages.

Donepezil, the most commonly prescribed of the dementia drugs, is licensed for people with mild to moderate Alzheimer’s disease. With limited evidence for effectiveness beyond this stage, the National Institute for Health and Care Excellence (NICE) had advised doctors to stop prescribing donepezil when the disease progressed to the moderate-to-severe stage.

Memantine had been licensed for use in moderate to severe AD - but was previously not recommended by NICE, other than for patients unable to tolerate cholinesterase inhibitors or people taking part in clinical studies.

DOMINO-AD set out to investigate whether patients with moderate to severe AD would have better cognitive and functional outcomes after 12 months treatment with donepezil, memantine or a combination of the two. The trial assessed whether AD patients with moderate to severe AD, who were already receiving donepezil, benefited from continuing treatment and whether initiating memantine at this stage conferred benefits.

Study summary:
As part of the randomised, double-blind, placebo controlled trial - 295 community living participants were recruited across the UK and assessed over a period of 12 months.

All participants had moderate-to-severe Alzheimer’s disease; had been prescribed donepezil continuously for at least 3 months prior to enrolment; and had caregivers who either lived with them or visited them daily.

Participants were randomly assigned to one of four treatment groups: donepezil and memantine, memantine only, donepezil only, or placebo.

Co-primary outcomes were scores on the Standardised Mini-Mental State Examination (SMMSE) - measuring cognition; and on the Bristol Activities of Daily Living Scale (BADLS) - measuring functional ability; with a range of secondary outcomes also assessed.

Clinical Research Network (CRN) support
With NIHR CRN support, the study took place across 26 hospital sites - with 13 Local Clinical Research Networks (LCRNs) supporting recruitment.

Professor Rob Howard, Chief Investigator of DOMINO-AD said: “The study was unusually difficult to recruit to. It involved approaching carers and patients with moderate to severe Alzheimer’s disease, who were understandably
anxious about being asked to potentially give up a treatment that they believed might have been working.

“The recruitment support provided by the CRN was invaluable in helping us achieve the participant numbers we needed. We were able to recruit sufficient numbers to show clinically important differences between the different treatment approaches.”

RESULTS

Cognition and function

Over the course of 12 months, patients who continued to take donepezil showed considerably less decline in cognition and function than those taking the placebo. The benefits of continued treatment were shown to exceed the minimum clinically important difference set for cognition.

Starting memantine treatment also resulted in significantly better cognitive and functional outcomes compared with those taking placebo - although the magnitude of benefit was less than that from continuation of donepezil.

Combined treatment with memantine and donepezil produced small benefits, although these were not found to be significantly superior to donepezil alone.

Nursing home placement

DOMINO-AD was the first trial to show a significant effect of dementia drug treatment on nursing home placement, determined as part of secondary, post-hoc analyses.

Patients with moderate to severe AD who continued donepezil treatment were shown to be at reduced risk of nursing home placement during the first 12 months (following randomisation) compared to those discontinuing donepezil. Statistically significant benefits were not maintained after 12 months, at which point the patients’ treating physicians chose their treatment.

No effect on nursing home placement was observed for those starting memantine against those who were not.

Cost effectiveness

Treating patients with donepezil and/or memantine was shown to be extremely cost effective in terms of the QALYs achieved - bringing significant financial benefits to the NHS. Since the study took place, both treatments have come off patent and now cost in the region of a few pence per day.

IMPACT

DOMINO-AD was the first trial to demonstrate the value of continued drug treatment for patients with moderate to severe AD.

The study provided vital evidence which directly led to a significant change to NHS clinical dementia guidelines, published by NICE in 2018.

As a result of the findings, the NICE guidelines recommend that clinicians should not stop the use of cholinesterase inhibitors, such as donepezil, because of dementia severity.

The guidelines also recommend that clinicians should consider combined memantine and cholinesterase inhibitors for patients with moderate AD, and offer the dual treatments to patients if they have severe disease (for those already taking an acetylcholinesterase inhibitor).

Professor Howard said: “DOMINO-AD was unique in terms of dementia trials in that a minimum clinically important difference around cognition and function was pre-set - and surpassed - in the case of the cognitive benefits evident with continuation of donepezil.

“The study has made a significant impact, not just within the NHS - but globally. It has provided robust evidence that has enabled treatment with these drugs to continue in patients who are in the later, more severe stages of Alzheimer’s disease - bringing significant benefits in terms of cognition.”

Key publications:


The Lancet Neurology: Nursing home placement in the Donepezil and Memantine in Moderate to Severe Alzheimer’s Disease (DOMINO-AD) trial. www.thelancet.com/journals/laneur/article/PIIS1474-4422(15)00258-6/fulltext

NICE guideline: Dementia: assessment, management and support for people living with dementia and their carers 2018. www.nice.org.uk/guidance/ng97

“In the UK alone, the change to clinical practice that has come about as a direct result of DOMINO is helping to improve the lives of many thousands of people with moderate-to-severe Alzheimer’s - along with their families and carers.”

Professor Rob Howard, Chief Investigator, DOMINO