In patients with Alzheimer's disease, what are the benefits of anti-dementia drugs?

Bottom line (11th July 2018):

While the group had entered into this question with a view that they would like to support optimal deprescribing of donepezil/memantine, a limited evidence based was identified. From the evidence examined, the group felt that while there was not strong evidence of benefit, the signal to benefit of donepezil (mental state test and activities of daily living) and the signal to harms (nursing home admission) within the first year of stopping, made the clinicians feel cautious about deprescribing in the absence of any other reason to (e.g. if patients could not take medications or if having adverse effects). The group were less convinced of the benefits of commencing memantine, however, the evidence was very limited.

Context:

Clinicians highlighted uncertainties about the value of medications for dementia. Newer models of working, including a pharmacist, was reportedly not making a clear headway in deprescribing medications, including dementia drugs. The group questioned what is the optimal stage to stop taking anti-dementia agents? They were not clear. The group wanted to investigate the question:

In patients with Alzheimer's disease, what are the benefits of anti-dementia drugs

i) For mild, moderate and severe disease?
ii) Being continued beyond 12 months?
iii) When disease transitions to severe?

PICO:

POPULATION: Patients with Alzheimer's dementia

INTERVENTION: ≥12 months dementia medication

COMPARATOR: no anti-dementia medication

OUTCOME: function

Evidence sources:

Using the TRIP database autosynthesis function (in development) for dementia (https://www.tripdatabase.com/autosynthesis?criteria=dementia&lang=en) which plots evidence for treatment on a y-axis of effectiveness (more to less) and various possible x-axes including risk of bias (low to high). The group were surprised to see memantine and donepezil as featuring in a medium risk of bias and near the less effective end of the scale with other, non-pharmacological approaches appearing more effective. However, the group was warned that this autosynthesis should be interpreted with caution.

The search was **(dementia)((donepezil OR memantine) AND (continuation OR continued OR continue))((donepezil OR memantine) AND (cease OR cessation OR**

stop OR stopping) which produced 61 results for a variety of types of evidence. On brief review of the results, many of them were relevant to the question but many referred to the DOMINO and subsequent DOMINO-AD study (Howard R et al; see below). Further, the NICE CKS guidelines were referenced and details of an ongoing systematic review. The group, therefore decided to look at the two papers most frequently referenced within the TRIP database search:

- Howard R, McShane R, Lindesay J, Ritchie C, Baldwin A et al. Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease. N Engl J Med. 2012;366:893-903. https://www.nejm.org/doi/full/10.1056/NEJMoa1106668 (DOMINO)
- Howard R, McShane R, Lindesay J, Ritchie C, Baldwin A et al. Nursing home placement in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD) trial: secondary and post-hoc analysis. Lancet Neurol. 2015:14:1171-81. https://linkinghub.elsevier.com/retrieve/pii/S1474-4422(15)00258-6

The Cochrane Library was also found to contain:

- 2018 Updated Review of *Donepezil for dementia due to Alzheimer's disease* by Birks et al http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD001190.pub3/abstract [Not presented at the meeting but for information – Authors' conclusions: There is moderate-quality evidence that people with mild, moderate or severe dementia due to Alzheimer's disease treated for periods of 12 or 24 weeks with donepezil experience small benefits in cognitive function, activities of daily living and clinician-rated global clinical state. There is some evidence that use of donepezil is neither more nor less expensive compared with placebo when assessing total healthcare resource costs. Benefits on 23 mg/day were no greater than on 10 mg/day, and benefits on the 10 mg/day dose were marginally larger than on the 5 mg/day dose, but the rates of withdrawal and of adverse events before end of treatment were higher the higher the dose.]
- 2016 Review of *Memantine for dementia* by McShane R et al (note part of DOMINO studies above and below) http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD003154.pub5/abstract;jsessionid=C20ACDCE92D3D1EC64347258F915C839.f02t01
  [Not presented at the meeting but for information – Authors' conclusions: Memantine has a small beneficial effect at six months in moderate to severe AD. In patients with mild to moderate dementia, the small beneficial effect on cognition was not clinically detectable in those with vascular dementia and was detectable in those with AD. Memantine is well tolerated.]

Impact:

How can we rationalise our statin use for primary prevention among our patients?

Bottom line (1st January 2017)

Having looked at primary evidence and a systematic review examining the impact of statin use among older adults and among those categorised as lower and higher CHD risk, the EBP group felt that the evidence was inadequate to change their practice, nor to help them to operationalise the NICE (CG181) guidelines.

Context:

Over recent years, atorvastatin has come off patent and has become cheaper and recent guidelines suggest this as a first line statin for primary and secondary prevention of cardiovascular disease. Some patients remain on traditionally cheaper statins, simvastatin, others are not on statins. There is some uncertainty also about when to stop statins, as tools such as QRISK do not calculate risk over 85 years.

NICE (CG181) suggest we:

People up to and including 84yr:	**Use QIRSK2 to assess CVD risk for primary prevention of CVD**	**"*Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool.*"**
People aged 85 or older:	**Consider these people to be at increased risk of CVD because of age alone, particularly people who smoke or have raised blood pressure**	**"*For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction. Be aware of factors that may make treatment inappropriate (see recommendation 1.3.12 - The decision whether to start statin therapy should be made after an informed discussion between the clinician and the person about the risks and benefits of statin treatment, taking into account additional factors such as potential benefits from lifestyle modifications, informed patient preference, comorbidities, polypharmacy, general frailty and life expectancy).*"**

However, as clinicians it feels inappropriate at times to be commencing and/or continuing some oldest old people on statins. We are also keen to avoid polypharmacy and over-treatment with limited benefit. We wanted to find out the evidence for use of statins and how best to rationalise prescriptions to support clinical conversations about prescribing and deprescribing.

Inclusion/exclusion:

Not applicable – the group examined 2 source papers, a recent paper specifically focussing on older adults (paper 1) and a systematic review using papers included in a Cochrane review of statins (paper 2)

PICO:

Not applicable – the group examined 2 source papers, a recent paper specifically focussing on older adults (paper 1) and a systematic review using papers included in a Cochrane review of statins (paper 2)

Evidence sources:

1. Han BH Sutin D, Williamson JD, Davis BR, Piller LB, Pervin H, Pressel SL, Blaum CS, for the ALLHAT Collaborative Research Group. Effect of statin treatment vs usual care on primary cardiovascular prevention among older adults. The ALLHAT_LLT randomised clinical trial. JAMA Intern Med. 2017. Doi:10.1001/jamainternmed.2017.1442.

   Real time critique summary (using CASP RCT checklist tool): the group stopped after the first three questions on the CASP checklist as they had significant uncertainties about the paper. Further, to get this far, the group had to refer to the ALLHAT protocol on the ALLHAT website, to seek adequate information to understand the study.

   - While the trial did address a clearly focussed issue, the usual care comparator included people also taking satins. By the end of year 6, nearly a third of patients were taking statins (we were not told what type or dose). Further, there were some inconsistencies in the dosing of pravastatin in the intervention arm, despite what the protocol said, the paper suggested 500 people were started on 20mg pravastatin rather than 40mg, which the rest of the patients were started on.
   - While the randomisation method was unclear in the paper, referring to the protocol revealed this to probably be to gold standard, using random assignment on the telephone. There also appeared to be some stratification, for the main ALLHAT trial, stratification on race was undertaken (this part of the trial was a subgroup of the ALLHAT trial).
   - There was a lack of clarity about what happened to the patients in the intervention and control arms. There was a flow chart but this only took readers to the randomisation. From 3 years, there appeared to be a significant drop in numbers of patients, from the data given alongside the figures.
   - Finally, the study protocol online outlined the sample size calculation was based on 20,000 patients, a 30% drop in cholesterol and baseline LDL of 155. Tin the end there was only 1,400 people in each arm, with drop in cholesterol of 25% and mean LDL at baseline around 147.
   - All of the above points are likely to lead to the study being underpowered to detect a change between the groups, further, given the use of statins among the control group and the cessation of statins in the intervention group, it was not entirely clear what the absolute difference between the groups were. So the group did not continue to critique the study.
2. Rossignol M, Labrecque M, Cauchon M, Breton MC, Poirier P. Number of patients needed to prescribe statins in primary cardiovascular prevention: mirage and reality. Fam Pract. 2017. Doi:10.1093/fampra/cmx124.

   Real time critique summary (using CASP SR checklist tool): the group felt that the conclusions of the paper could not be entirely supported due to a number of reasons:

   - Methodological uncertainties – there was inconsistency within the definition of persistence and within the stratification of risk, which, although described, the rationale was not made entirely clear within the paper
   - Lack of clarity about alignment of the interventions with current national guidelines (the papers were old 1990s-2011) – for example, sometimes the statin group included co-prescription of warfarin, thiazide and different statin dosages

- The authors had excluded symptomatic CHD (e.g. angina) from the outcomes, only including non-fatal and fatal MI and CHD deaths. While the authors explained their rationale was an inconsistency in definitions of these events, the group felt this group of patients was important to primary care clinicians.
- More evidence was felt to be required before practice could be changed.

Impact:

The group decided that these papers did not provide evidence that would result in them changing their practice.