Cholinesterase inhibitors—statistically significant versus clinically important differences?

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TRIAL RESULTS OVER THE LAST 10 YEARS: There have now been many clinical trials of cholinesterase inhibitors in people with early Alzheimer's disease, severe Alzheimer's disease and mild cognitive impairment in order to try to find a place for these medicines in dementia. The studies have been very disappointing, as reflected in systematic reviews.

MAIN FINDINGS: Outcome domains in the clinical trials involve measures of cognition, global function, behaviour/mood and quality of life/activities of daily living. These trials have found statistically significant differences in some cognition tests favouring cholinesterase inhibitors, but the absolute differences are very small and mostly do not achieve a clinically relevant improvement. For example, to show a beneficial clinical effect on the Alzheimer's Disease Assessment Scale there needs to be an improvement of four or more points on a 70-point scale; or the MMSE needs to improve three or more on a 30-point scale.

FOR WHOM MIGHT DONEZEPIL BE EFFECTIVE? The APO$\varepsilon_{\varepsilon 4}$ allele is a major predictor of Alzheimer's disease and carriers of this appear to benefit the most from donezepil.

ADVERSE EFFECTS: Adverse effects are usually dose-related and are typical cholinergic effects:

- Nausea, vomiting, diarrhoea (up to 10%)
- Insomnia—increased sedative use (up to 9%)
- Myalgia/pain (up to 9%)
- Urinary incontinence
- Sweating
- Syncope
- Bradycardia—increased pacemakers insertions
- Headache
- Leg cramps
- Abnormal dreams
- Hip fracture
- Psychiatric disturbances, such as agitation, which are difficult to separate from the progression of the dementia.

CAUTION IN PEOPLE WITH:

- A risk of peptic ulcer disease
- A history of seizures
- Asthma or COPD
- Low body weight.

WHAT TO TELL THE PATIENT AND FAMILY:

- There is no cure for Alzheimer's disease
- Medicines may help symptoms but the impact is minor, not usually observable and only temporary
- There are many adverse effects from the medicines
- Non-medicine techniques may have a better effect.

OTHER CONSIDERATIONS WHEN DEMENTIA IS DIAGNOSED:

- Try to remove any medicines with anticholinergic effects. This includes a review of antipsychotic medicines being used for agitation
- Discuss Enduring Power of Attorney
- Discuss Advanced Directives
- Review medicines and consider the benefits of primary and secondary prevention medicines (quality of life versus quantity of life).

AUTHOR'S CONCLUSIONS: Cholinesterase inhibitors have significant adverse effects and the clinical importance of any improvement in cognitive scores is marginal. The people in whom they may be most useful are those with the APO$\varepsilon_{\varepsilon 4}$ allele.

The first step for people with Alzheimer's disease is to stop anticholinergic medicines.

References available on request

KEY POINTS

- Cholinesterase inhibitors such as donezepil may result in statistically significant improvements in some cognitive scales, but the increases are generally too small to provide any clinically relevant improvement
- Studies of cholinesterase inhibitors have mainly been less than 12 months with high withdrawal rates, leaving the question of persistence of any potential delaying effect unanswered
- There is no apparent benefit in the use of cholinesterase inhibitors in mild cognitive impairment to delay the onset of dementia or Alzheimer's disease
- Adverse effects from cholinesterase inhibitors are high—gastrointestinal (up to 10%), CNS (insomnia, psychiatric disturbances), sweating, bradycardia, myalgia, nightmares, urinary incontinence, headaches, syncope
- Stopping anticholinergic medicines would have a better impact on dementia.

NUGGETS *of* KNOWLEDGE provides succinct summaries of pharmaceutical evidence about treatment of common conditions presenting in primary care and possible adverse drug reactions.