## DEMENTIA

**Prescribing for Alzheimer's disease in primary care** DTB2014;52;69

Although current NICE guidance is that these drugs should be initiated by a specialist, in many parts of the UK responsibility for the continued prescription of these drugs is being transferred to primary care. We find ourselves with a number of learning needs: *when should they be started, which drug, dose changes, common side effects, any benefit from switching and when should they be stopped?*

The DTB recently reviewed the evidence. They remind us that there are *currently no interventions that cure or alter the long-term progression of dementia.*

All of the available drugs have modest efficacy but are generally well tolerated. The four approved and licensed available drugs are:

- **The acetylcholinesterase inhibitors (AChEIs): donepezil, galantamine and rivastigmine**
    - Licensed and approved by NICE as recommended options for mild to moderate AD
- **Memantine** (a different mode of action, an NMDA antagonist)
    - Licensed and approved by NICE as an option for moderate to severe AD, and for those who cannot take AChEIs

***How effective are they?***

- **AChEIs:** there is level 1a evidence from a systematic review of trials that compared to placebo they modestly improve cognitive function compared to placebo (by an average of 3 points on a 70 point scale, considered the minimal clinically significant change) in mild, moderate and severe disease
    - The NNT is 12 to achieve a significant benefit in cognitive function after 12 weeks
    - The NNH is also 12 over the same time to have an adverse effect
    - Modest benefits are also seen for a range of other outcome measures, such as activity of daily living (ADL) and behaviour
    - One study has shown that when patients develop severe AD, continued treatment with donepezil (as compared to stopping it) is worthwhile in terms of preserving cognition and function
- **Memantine:** there is level 1a evidence that Memantine has a small beneficial effect in moderate and severe AD, but not in mild AD
    - At 6 months benefits were seen in cognition, mood, behaviour and ADL
- Combination treatment of AChEI and memantine: studies have shown conflicting results, but a meta-analysis (1a) failed to show clinically significant benefit for combination therapy

Whilst these mean effects seem modest, another paper BMJ2012;344:e2986 highlighted

- The modest overall benefit hides the fact that a small number of patients derive a substantial benefit whereas most do not, encouraging a 'trial of treatment' approach.
- There is evidence that at 6 months patients on donepezil worsen less than on placebo (NNT of 6), so apparent 'non-responders' may still be getting some benefit compared to placebo.
- Some authors then feel that a positive response to treatment would be considered 'reduced worsening than expected if left untreated'

***What about adverse events?***

- AChEIs: cholinergic stimulation commonly causes nausea, vomiting, diarrhoea, headaches and insomnia
    - These adverse effects tend to occur at the start of therapy or dose increases and are often transient; slow dose titration or dose reduction will often help

- More significant side-effects include:
  - Tremor, urinary incontinence, agitation, abnormal dreams, hallucinations
  - Bradycardia due to a vagotonic effect on the heart can occur, especially in poatients with 'sick sinus syndrome' or on other rate-limiting drugs
    - Do not use if resting HR is <50 bpm
    - Monthly monitoring of HR advised in the titration stage, thereafter 6 monthly
  - They may cause bronchoconstriction in asthma and COPD, and be used with caution in patients with a history of peptic ulcer
- Memantine can cause sedation, dizziness, constipation, headache and hypertension
  - It should also be used in caution in epilepsy

***What about clinically important interactions?***

- AChEIs: Concomitant use of the following should be avoided
  - anti-cholinergic drugs, which may negate their effect
  - Rate limiting drugs e.g. beta blockers, amiodarone, calcium channel blockers etc
  - Donepezil and galantamine are metabolised by cytochrome P450, so adverse effects are increased by enzyme blockers (e.g. erythromycin, fluoxetine) and efficacy reduced by inducers (e.g. phenytoin, carbamazepine etc). Rivastigmine is not metabolised by hepatic enzymes so is free of these interactions.
- Memantine may enhance the effect of levodopa and dopaminergic drugs

**When should they be stopped?**

- NICE guidance is that drugs should only be continued when it is considered to be having a worthwhile global effect on cognitive, functional or behavioural symptoms
- Treatment should be reviewed on a regular basis to assess if this is still the case
- GPs should not rely solely on cognitive scores and the decision to continue or stop should be based on a 'holistic' assessment and incorporate patient (wherever possible), family and carers' views

***What about prescribing in other forms of dementia?*** **BMJ2012;344:e2986**

AD is thought to account for 60% of dementia cases. The most common other forms are:

- Vascular dementia
- Mixed dementia
- Dementia with Lewy bodies
- Parkinson's disease dementia
- Pick's disease (frontotemporal dementia, a severe sub-type characterised with aphasia)

The most convincing evidence is for **anticholinesterase inhibitors in Lewy Body and Parkinson's**, especially rivastigmine.

There is evidence of a modest benefit in vascular dementia, but the drugs are not licensed or approved for this. In practice, vascular dementia and AD are often 'mixed' so a trial of treatment may be warranted.

There is evidence that the drugs are NOT of benefit in mild cognitive impairment and in frontotemporal dementia.

## KISS Summary of Dementia Drugs

**Based on** DTB2014;52;69 **and** BMJ2012;344:e2986

| Drug and approx.. monthly cost | Dosage regimen | Common side effects | Important interactions |
|---|---|---|---|
| **Donepezil**<br>£1.60 tablets, £12 for oro-dispersible form<br><br>***First choice drug due to low cost and weight of evidence***<br><br>(For mild to moderate AD, and dementia with Lewy bodies. May be continued in severe AD off-license with specialist guidance) | 5mg daily, increased after 1 month if needed to a max of 10mg daily | ***Serious side-effects are rare***<br>GI (nausea, vomiting, diarrhoea, anorexia) side-effects common and dose-related. Also:<br>Headaches, insomnia<br>Bradycardia (caution with AV block; monthly monitoring at onset, stop if HR<50)<br>Tremor, agitation, dreams, hallucinations<br>Caution with asthma, COPD, urinary retention and peptic ulcer | Anti-cholinergic and rate limiting drugs<br>P450 inhibitors and inducers |
| **Galantamine**<br>£74<br>£79 extended release<br>£200 oral solution<br><br>(For mild to moderate AD, and dementia with Lewy bodies) | 4mg bd for 4 weeks, then 8mg bd for 4 weeks, then 8-12mg bd maintenance dose<br>extended release: 8mg daily, then 16mg daily after 4 weeks,maintenance 16-24mg daily | ditto | ditto |
| **Rivastigmine**<br>£33 capsules, £73 patch<br><br>(For mild to moderate AD, and dementia with Lewy bodies. Also Parkinson's disease dementia) | 1.5mg bd, increase by 1.5mg at 2 weekly intervals to maximum of 6mg bd<br>patch: 4.6mg/24 hours increase after 4 weeks to 9.5mg/24 hours; can increase to 13.3mg/24 hours after 6 months if meaningful decline | Ditto<br>GI side effects are less with the patch | ditto, but no problem with hepatic enzyme blockers or inducers (so fine with phenytoin, carbamazepine etc) |
| **Memantine**<br>£28 tablets, £67 solution<br><br>(For moderate to severe AD) | 5mg daily, increase by 5mg every week to a maximum of £20mg daily | Fewer and less serious side-effects than the AChEIs.<br>Constipation, headache, somnolence, dizziness most common s/e | May enhance levodopa |