Current Treatments for Dementia and Future Prospects

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# Dementia

## Cognitive
- Memory
- Orientation
- Language
- Other cognitive abilities
  - Planning
  - Organising
  - Problem solving
- Praxis

## Non-cognitive (BPSD)
- Behavioural symptoms
  - Agitation
  - Wandering
  - Apathy
- Psychotic symptoms
  - Delusions
  - Hallucinations
- Affective
  - Depression
Treatment of cognitive symptoms
Available drugs

• Acetylcholinesterase inhibitors (ACHIs)
  – donepezil (Aricept)
  – rivastigmine (Exelon)
  – galantamine (Reminyl)

• NMDA agonist
  – memantine
A problem.....

- Evidence is confusing
  - 5 outcomes
  - 4 drugs
  - 3 diseases
  - 2 stages
## Efficacy of ACHIs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Number needed to treat</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>donepezil</td>
<td>10mg</td>
<td>4</td>
<td>+</td>
</tr>
<tr>
<td>rivastigmine</td>
<td>6mg bd</td>
<td>5</td>
<td>+++</td>
</tr>
<tr>
<td>galantamine</td>
<td>12mg bd</td>
<td>7</td>
<td>+</td>
</tr>
</tbody>
</table>
• Sustained effects up to 240 weeks
  – Improved over baseline for 38 weeks
  – Benefit over placebo sustained
• mild-moderate dementia
  – Delays functional decline in by 5 months (NNT 7)
  – No effect on Quality of life

• moderate-severe dementia (MMSE 5-17)
  – Improve global state, preserves ADLs, and reduce carer stress
Memantine

- Moderate to severe AD.
  - Marginal improvements on cognition and ADL
- Mild to moderate AD.
  - Marginal improvement on cognition
    - ADAS-cog 0.99 (0.21 to 1.78)
  - no significant effect on behaviour or activities of daily living
- Few side effects
Other treatments for dementia

current evidence-base

<table>
<thead>
<tr>
<th>drug</th>
<th>Alzheimer’s</th>
<th>vascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>oestrogen</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>+/-</td>
<td>?</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Statins</td>
<td>?</td>
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</table>
Non-drug treatments

• Reminiscence therapy
• Music therapy
• Reality orientation
• Exercise
• Cognitive training
Dementia

Supporting people with dementia and their carers in health and social care
NICE recommendations

- Alzheimer’s disease only
- MMSE 10-20 (but caveats)
- Specialist initiation
- Least expensive drug
- Review (MMSE, function and behaviour) 6-monthly (can be by GP)
- Continue while MMSE remains 10+
Problems with NICE

- Alzheimer’s disease only
  - Evidence for other dementias is mounting
- Not recommended for mild dementia
- Decision based on QALYs
  - QoL does not improve with ACHIs
- Overlooks individual impact
- Stopping if MMSE < 10 is problematic
### Proportion with AD receiving ACHIs

<table>
<thead>
<tr>
<th>Country</th>
<th>percentage</th>
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<tbody>
<tr>
<td>Italy</td>
<td>84%</td>
</tr>
<tr>
<td>Spain</td>
<td>76%</td>
</tr>
<tr>
<td>Japan</td>
<td>68%</td>
</tr>
<tr>
<td>US</td>
<td>64%</td>
</tr>
<tr>
<td>France</td>
<td>61%</td>
</tr>
<tr>
<td>Germany</td>
<td>55%</td>
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Source: Alzheimer Europe 2007
Proportion with AD receiving ACHIs

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<td>55%</td>
</tr>
<tr>
<td><strong>UK</strong></td>
<td><strong>33%</strong></td>
</tr>
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Source: Alzheimer Europe 2007
Prescribing Observatory for Mental Health

- 2007 audit of 19 Trusts (54 PCTs)
  - 1897 patients
Prescribing Observatory for Mental Health

- 2007 audit of 19 Trusts (54 PCTs)
  - 1897 patients
- 13% of eligible people received ACHIs
  - 67% donepezil
  - 20% galantamine
  - 9% rivastigmine
- 50% prescribed in primary care
Why are ACHIs not used?

• NICE guidance is too restrictive?
• Cost considerations?
• Lack of shared care?
• Concerns about evidence?
Unanswered questions

• Can we predict who will respond?
• How long do the drugs work for?
• Is one CI better than another?
• Is earlier treatment relatively better?
• Do ACHIs work in other types of dementia?
• If one doesn’t work, is it worth trying another?
Recommendations

• Do not let drugs dominate dementia care
  – Maintain holistic approach
• All patients with AD/VaD should have trial
  of donepezil or galantamine
• Review after 3-6 months and stop if not
  effective
• Do not rely on MMSE or NICE to guide
  decisions on treatment
Behavioural and Psychological Symptoms of Dementia (BPSD)
“One of the first disease symptoms of a 51-year-old woman was a strong feeling of jealousy towards her husband. Very soon she showed rapidly increasing memory impairments; she could not find her way about her home, she dragged objects to and fro, hid herself, or sometimes thought that people were out to kill her, then she would start to scream loudly.”
“From time to time she was completely delirious, dragging her blankets and sheets to and fro, calling for her husband and daughter, and seeming to have auditory hallucinations. Often she would scream for hours and hours in a horrible voice.”
BPSD consequences

- Associated with greater functional impairment
- Very distressing for individual
- Very distressing for carers
- Institutional care
- Overmedication
- Elder abuse
- Associated with increased mortality
Treatment options

• Identify cause
• Wait and see?
• Education and counselling
• Prophylaxis
• Environmental modification
• Direct behavioural approaches
• Medication
BPSD Drug Treatment

• Risperidone and haloperidol are effective
  – Significant increased risk of stroke and death
• ACHIs- probably not effective
  – More studies needed
• Benzodiazepines- probably effective
  – More studies needed
• Carbamazepine- probably effective
  – More studies needed
BPSD management

• Drug treatment
  – Last resort
  – Should target *specific* symptoms
  – Specialist initiation
  – Regular review
The future
• Over 40 drugs in development
• Around 20 have potential disease modifying action
Amyloid overproduction

Deposition of amyloid (plaques)

Inflammatory response

Abnormal tau phosphorylation

Neurofibrillary tangles

DEMENTIA

β and γ secretase inhibitors

Anti A β immunisation

Anti-inflammatory drugs

Tau kinase inhibitors

Tau aggregation inhibitors

Cholinesterase inhibitors
conclusions

• Drug treatments must not become focus of management
• Good evidence for ACHIs in Alzheimer’s disease and Vascular dementia
  – donepezil and galantamine safe and well tolerated
• Drug treatment of BPSD is last resort
• Several exciting developments awaited
Thank You