East London and City Guidelines for use of Anti-Dementia Drug Treatments

Summary

In its January 2001 publication, **The National Institute for Clinical Excellence (NICE)** stated that the use of **Donepezil, Rivastigmine and Galantamine** should be made available by Trusts, Health Authorities and Primary Care Trusts for the treatment **Alzheimer's disease (AD).**

The following document sets out guidance for anti-dementia drug treatment in this district and uses the following NICE specified conditions for their use:

- The drugs form one component of the management of people with mild to moderate AD, whose mini mental state examination (MMSE) score is above 12 points.

- The diagnosis of AD must be made in a specialist clinic according to standard diagnostic criteria. Assessment of cognitive, global and behavioural functioning and activities of daily living should be made before the drug is prescribed. The likelihood of patient compliance needs to be ensured.

- Only specialists (including Old Age Psychiatrists, Neurologists, and Care of the Elderly Physicians) should initiate treatment. The Carer's view of the patient's condition at baseline and follow up should be sought. General Practitioner prescribing is recommended only within an agreed shared-care protocol with clear treatment end points.

- Assessment of improvement, 2 – 4 months after reaching a maintenance dose, should be made. The treatment should continue only if there has been an improvement or no deterioration in MMSE, together with evidence of global improvement on the basis of behavioural and /or functional assessment.

- While the MMSE score remains above 12 and patients seem to be benefiting overall, patients should continue the treatment and should be reviewed by MMSE score and global, functional and behavioural assessment every 6 months. When the MMSE score falls below 12 patients should not normally be prescribed the drugs. Reviews involving MMSE assessment should be undertaken by appropriate specialist teams, unless there are locally agreed protocols for shared care.

The following guidelines will expand on these conditions and include: **Criteria for diagnosis of Alzheimer's disease/ Drug mode of action, dose and costs/ Treatment guidance and algorithm / Patient suitability guidance and care pathways/ Treatment Audit Monitoring Form/ Assessment Scales/Patient Information Leaflet .**

Criteria for diagnosis of Alzheimer's disease

Clinical criteria for the diagnosis of AD include insidious onset and progressive impairment of memory and other cognitive functions. Non-cognitive disturbance can include personality change with suspicious and unstable mood, restless and aggressive behaviour and psychotic symptoms.

There are no motor, sensory or coordination deficits early in the disease. The diagnosis cannot be determined by laboratory tests. These tests are important primarily in identifying other possible cases of dementia that must be excluded before the diagnosis of AD can be made with confidence.

Many clinicians use the ICD-10 criteria although the subjects included in the drug trials were required to meet the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association) diagnostic criteria for 'Probable Alzheimer's disease'. This includes:

1. The presence of a dementia syndrome with evidence of deterioration in two or more areas of cognition (e.g. memory, orientation, attention, abstract thinking, judgement, comprehension, language, recognition, calculation, motor skills, constructional and visual-spatial function)

2. A progressive worsening of memory and other cognitive function.

3. No disturbance of consciousness.

4. The absence of systemic or brain diseases that in and of themselves would account for these deficits.

5. The diagnosis is supported by features such as; positive family history, progressive deterioration of specific cognitive features, such as speech or motor skills (aphasia and dyspraxia), and evidence of cerebral atrophy on CT.

The need to exclude depression and other dementias including vascular dementias lends support to the NICE condition for the diagnosis to be made by specialists who have experience in managing dementias. The use of the Modified Hachinski Ischaemia Scale can help to differentiate AD from vascular dementia. A score of 4 or less is in favour of the diagnosis of AD.

There is agreement amongst clinicians that a full history from patient and carer, mental/cognitive state examination, physical examination and dementia blood screen (FBC, B12 and Folate, U&Es, LFTs, TFTs, and VDRL) is mandatory, though less regarding CT scans, as they cannot confirm or exclude AD. Nevertheless many clinicians value the use of CT to exclude other brain diseases.

Anti-dementia drug mode of action, dose and costs

Donepezil, rivastigmine and galantamine all inhibit the enzyme acetylcholinesterase (AChE) thereby raising the concentration of acetylcholine at sites of neurotransmission.

Their mode of action can be differentiated as follows:

Donepezil (Aricept) is a piperidine and a reversible AChE inhibitor. It has a linear dose-response relationship and a half-life of 70 hours with no active metabolites and is given once daily at 5-10mg.

Rivastigmine (Exelon) is a carbamate and a pseudo-irreversible AChE inhibitor. It has a half–life of 10 hours with no active metabolites and is given twice daily at 6-12mg/day.

Galantamine (Reminyl) is a tertiary amine and a reversible inhibitor of AChE and modulator of pre-synaptic nicotinic receptors. It is derived from narcissi and snowdrops. It has a half–life of 6 hours with no active metabolites and is given twice daily at 8-24mg/day.

In all the trials a 'response', i.e. a statistically significant improvement in cognitive function and effect on global outcome measures, was found in an average of 40% with low numbers needed to treat e.g. a NNT

for Donepezil of 4, Rivastigmine of 7 and Galantamine 3. The cognitive response, has been shown to last approximately 8 months, followed by a decline that remains significantly above that of the placebo group for longer periods.

Adverse effects of all three drugs include nausea, vomiting, diarrhoea and abdominal pain and are due to cholinergic transmission. These may be avoided in part by building up to a maximum dose slowly.

No guidance yet exists by which to select a specific drug. There is evidence however that, if benefit is shown at low dose, further benefit can be gained by increasing to the maximum recommended dose. Many patients and carers report functional benefits and improvements in behavioural symptoms on treatment, although galantamine is currently the only drug with a specific license for control of behavioural disturbance.

The annual cost at the maximum dose does separate the drugs, with donepezil at £1,248, galantamine £1049 and rivastigmine £ 879 (same for all doses).

Treatment Guidance

The NICE guidance states that the use of AChEIs should be considered in the context of comprehensive pathways of care, including that from carers and care-workers, social workers and other social services, nurses, GPs and other primary care workers, secondary care specialists and nursing homes. Specialist assessment will often require multidisciplinary team input including medical, nursing and occupational physiotherapy and psychologist expertise.

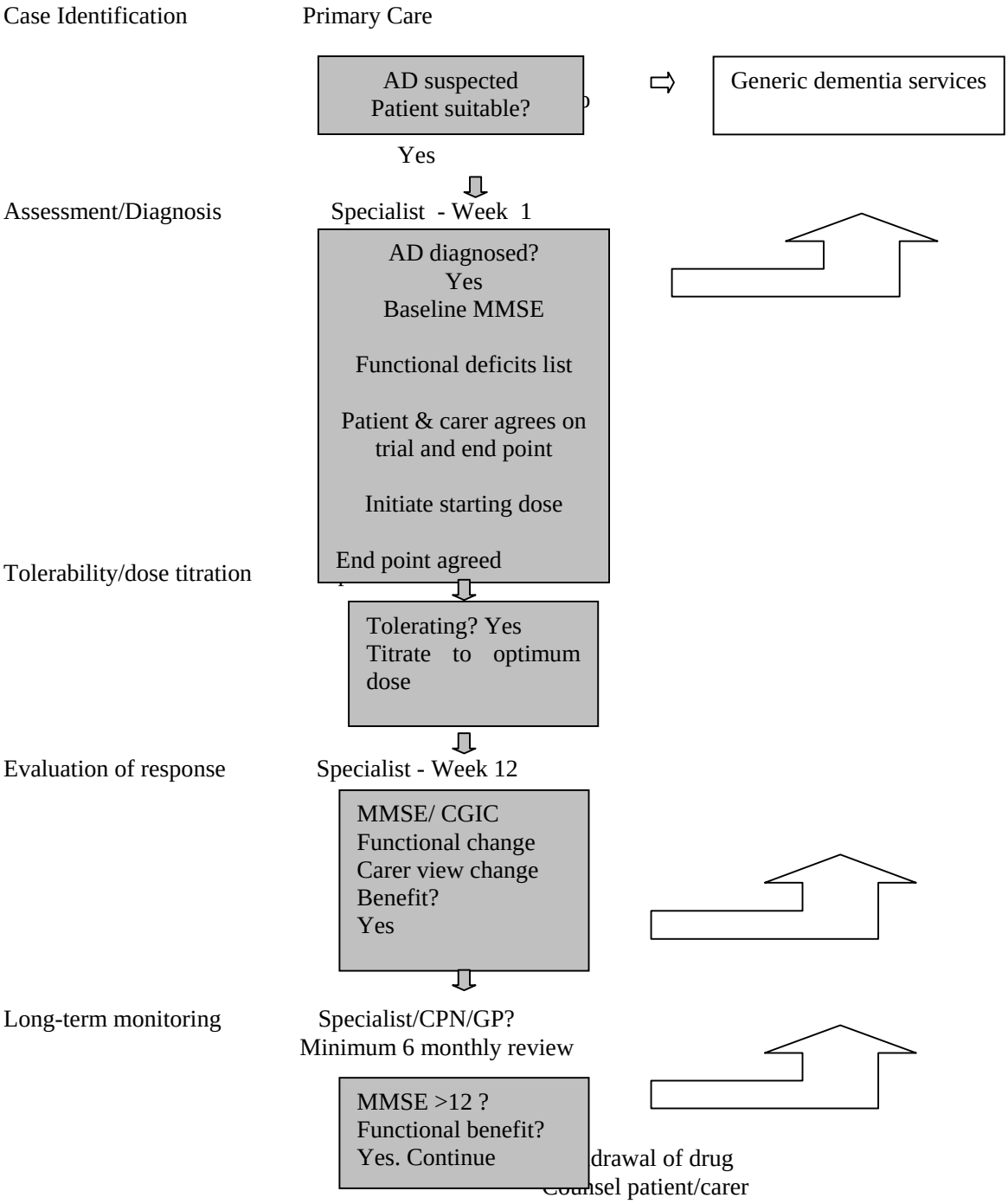
Memory clinics are described as the appropriate facilities to manage anti-dementia treatment. In East London Memory clinics are being developed to respond to the referral demand but full resources are not yet in place and therefore patients are also receiving specialist assessment and AChEI treatment initiation in existing settings including wards, generic clinics, day hospitals and the community.

It is expected that in addition to old age psychiatrists, neurologists and care of the elderly physicians will wish to initiate treatment from their specialist clinics and day hospitals. The specialist will confirm of the diagnosis of probable Alzheimer's disease either in a ward, day hospital, clinic or community setting. A CT head scan will usually be obtained to exclude other gross cerebral disease.

A baseline MMSE score and a list of target disabilities and behavioural symptoms will be noted. If a patient has a depressive illness this will be treated first. In addition to the MMSE score and evaluation of functional and behaviour change, the quick and simple tool, the Clinician's Global Impression of Change (CGIC) and the Carer's Rated Impression of Change (Carer-IC) is suggested in rating global effects at the evaluation visit at two to four months.

When it is established that a patient has responded to the AChEI treatment, the maintenance prescribing can transfer to primary care. Specialists should hold overall responsibility for long-term monitoring and termination of treatment although shared care protocols are in development. Community psychiatric nurses will provide the link between clinics and the community will often provide some of the MMSE and functional evaluation, as well as providing support and education.

Treatment Algorithm



Patient Suitability and Referral Guidance

Efficacy trials are on going including patients with Mild Cognitive Impairment, severe AD (MMSE <12), Dementia with Lewy Bodies, Mixed dementia and Vascular dementia. So far AChEIs have shown positive effects in Dementia with Lewy Bodies (McKeith et al, 2000) and it is anticipated they will be prescribed for this condition on occasions by local neurologists.

Although the NICE conditions currently exclude these patient groups, the document does state that the guidance does not override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

The following patient criteria should guide referrers and specialists considering AChEI treatment within the NICE conditions.

- Patients with insidious onset of memory impairment and confused behaviour who are suspected to have mild to moderate Alzheimer's disease (MMSE 12-26, AMTS>7/10). Patients with confusion of acute onset or dementia due to clear organic causes such as head injury, alcoholism and stroke disease or HIV are not suitable.

- Patients who are likely to benefit most will be living at home and still relatively independent or supported by local carers who can supervise medication and ensure compliance.

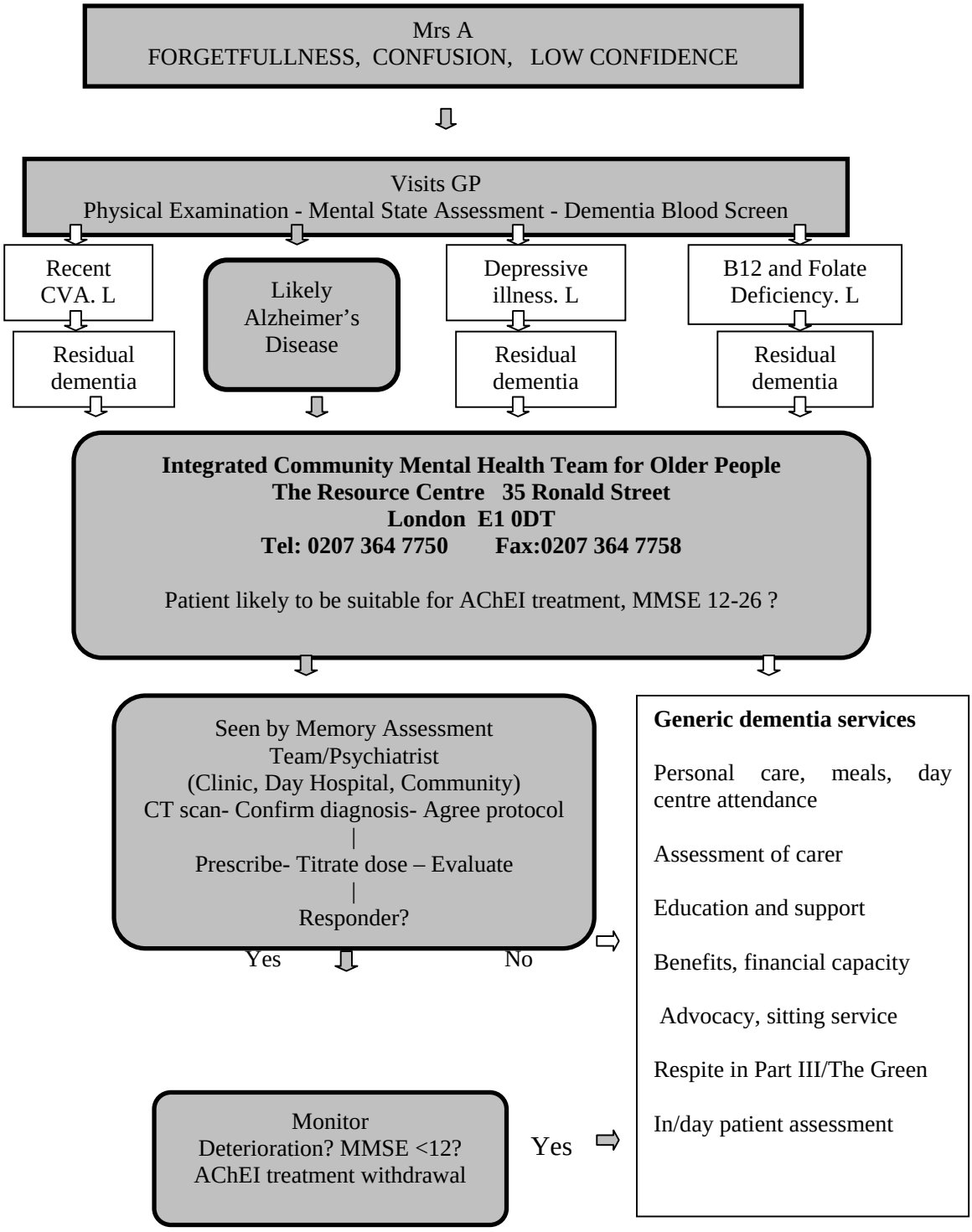
- Patients with severe cognitive impairment, serious medical problems, and those resident in nursing homes are unlikely to be suitable.

- Patients referred to specialists must come with a GP recommendation having had a preliminary assessment to exclude treatable medical conditions. Most GPs are able to complete a full dementia blood screen.

- The patient and carer are able to give an informed agreement to receive treatment and will receive written information explaining the treatment. They will agree to the protocol under which they will receive treatment and that treatment will be discontinued if there is no response or a decline at 3 months and later when the MMSE falls below 12 and no loss of function is demonstrated by withdrawal.

Those patients who are excluded by the above conditions as well as those who do not tolerate or respond to treatment or those responders who deteriorate on treatment beyond the discontinuation point will still be suitable for referral to and management by generic dementia care teams. The following care pathways illustrate dementia care variations in the three East London localities of City and Hackney, Newham and Tower Hamlets.

Dementia Care Pathways in Tower Hamlets



Specialist Assessment Audit Form for AChE Inhibitors

1. Patient Name: …….. 2. Hospital:…….
3. Number: ……... 4. Consultant:…….
5. Request for Referral:
   Consultant: ❒ GP: ❒ Other (Please State): ❒ ……

		YES	NO
6.	Depression excluded?	❒	❒
7.	Confirmed clinical diagnosis of probable Alzheimer's disease:	❒	❒
8.	Patient aware of protocol under which they will receive treatment	❒	❒
9.	Reliable care-giver able to supervise medication?	❒	❒
10.	Has full laboratory dementia screen assessment been completed?	❒	❒
11.	Has neuroimaging scan been undertaken?	❒	❒

		Baseline	4 wks	3 mths	6 mths	12 mths	18 mths
12	Hachinski Ischaemia Score						
13	Clinician rated global impression of change (CGIC)						
14	Carer rated impression of change (Carer-IC)						
15	MMSE						
16	Donepezil/Rivastigmine/ Galantamine						
	Dose						
17	Treatment continued Yes/No						

18. Reason for Treatment Discontinuation:

- Potential Benefit of treatment is no longer clinically significant in terms of the overall disease severity/stage ❒
- Withdrawal of consent ❒
- Poor compliance ❒
- Poor tolerability ❒
- Safety issues ❒
- Entry into Nursing/Residential care ❒
- Side effects:

  Nausea/Vomiting ❒ Diarrhoea ❒
  Gastric upset ❒ Constipation ❒
  Anorexia ❒ Fatigue ❒
  Agitation ❒ Flushing ❒
  Muscle Cramps ❒ Rhinitis ❒
  Other (please state) …… ❒

19. Unmet need and comments on non-cognitive benefits:

……
……
……

Assessment Scales

1. Modified Hachinski Ischaemia Scale

(Rosen et.al., 1980)

Abrupt Onset:	…	…	…	2
Stepwise Deterioration:	…	…		1
Somatic Complaints:	…	…		1
Emotional Incontinence:	…	…		1
History or Presence of Hypertension:			…	1
History of Stroke:	…	…		2
Focal Neurological Symptoms:	…			2
Focal Neurological Signs:		…	…	2

2. Carer Rated Impression of Change (Carer-IC)

Please mark a tick in ONE of the following boxes to indicate how the person you are looking after has changed since the last assessment:

	Score	
❒	1	Marked Improvement
❒	2	Moderate Improvement
❒	3	Minimal Improvement
❒	4	No change
❒	5	Minimal Decline
❒	6	Moderate Decline
❒	7	Marked Decline

3. **Clinician's Global Impression of Change**

Taking all factors into consideration (patient and caregiver reports, MMSE score and your clinical assessment of the patient), rate the degree of change in the patient condition since your initial evaluation:

	Score	
❒	1	Marked Improvement
❒	2	Moderate Improvement
❒	3	Minimal Improvement
❒	4	No change
❒	5	Minimal Decline
❒	6	Moderate Decline
❒	7	Marked Decline

Information sheet

Aricept, Exelon and Reminyl - the new drugs for Alzheimer's disease

Aricept, Exelon and Reminyl are not cures for Alzheimer's disease. However, they can temporarily slow down the progression of symptoms in people in the early to middle stages of the disease.

How do these new drugs work?

Research has shown that there is not enough of a chemical called acetylcholine in the brains of people with Alzheimer's disease. Acetylcholine is one of the chemicals nerve cells use to communicate.

Aricept, Exelon and Reminyl are called acetylcholinesterase inhibitors. They prevent an enzyme known as acetylcholinesterase from breaking down acetylcholine in the brain. Increased concentrations of acetylcholine lead to increased communication between nerve cells which may in turn temporarily improve or stabilise the symptoms of Alzheimer's disease.

How do the drugs differ from each other?

Aricept, Exelon and Reminyl work in similar ways. However, Reminyl also appears to act on the nicotinic neuronal receptors in the body, making them release more acetylcholine.

It is possible that one of these drugs might suit an individual better than another. The specialist should be able to advise whether there is any advantage associated with a particular drug.

Are they effective for all people with Alzheimer's disease?

At present Aricept, Exelon and Reminyl are only used in people with mild to moderate Alzheimer's disease. They are not effective for everyone and will only temporarily improve memory or delay memory loss.

Research is being undertaken to find out whether any of these drugs may be effective in the later stages of Alzheimer's disease.

Are there any side effects?

Not everyone has the same side effects or has them for the same length of time. The most frequent side effects include nausea and vomiting, diarrhoea, stomach cramps and headaches, dizziness, fatigue, insomnia and loss of appetite.

How and where can these drugs be obtained?

A government advisory committee, the National Institute for Clinical Excellence (NICE), has recommended that Aricept, Exelon and Reminyl should be available on NHS prescription for all those who could benefit.

In the first instance, these drugs can only be prescribed by a consultant. The GP will need to refer the person to a hospital for a specialist assessment. The consultant will carry out a series of tests to assess whether the person is suitable for treatment and will issue the first prescription if appropriate. Subsequent prescriptions may be issued by the GP or the consultant.

Some people may still wish to obtain these drugs privately. Private prescriptions can be obtained either through a consultant, a GP

or a private hospital. Private prescriptions are subject to consultation fees, prescription charges and dispensing fees which vary. The current cost of these drugs to the NHS ranges from £800 to £1,000 per patient per annum.

Whether these drugs are obtained on the NHS or privately, the person who is taking the drug must be willing to take the treatment. It is also important to discuss with the doctor any possible benefits, risks or side effects.

Are these drugs effective for other types of dementia?

This type of drug was developed specifically to treat Alzheimer's disease. We do not yet know whether they can be helpful for people with other forms of dementia, although there is evidence that they may be effective in dementia with Lewy bodies and even vascular dementia. Research is continuing.

What are the benefits of the drugs?

It is impossible to predict the potential benefits of using any of these drugs. Some people will improve, some will not, while others will continue to deteriorate.

In cases where these drugs prove effective they appear to slow down the progression of symptoms, including memory loss. They can also improve mood, reduce anxiety and restore confidence.

People who do not show an improvement or slowing down in the first few months are unlikely to show any benefit later on. In these cases the drugs will be stopped.

Taking the drugs

It may be helpful if the consultant seeks the carer's views of the person's condition before treatment and during follow-up appointments. The patient's views should also be sought. The consultant will also need to be sure that the patient takes their medication regularly.

Dosages vary. Usually a patient will start on a low dose which will be increased later to maximise effectiveness. It is important to be on the highest tolerable dose to get the maximum effect.

- Aricept is administered once a day and can be taken with or without food. It is available in 5mg or 10mg tablets.
- Exelon is taken twice a day, normally in the morning and evening. People start with 3mg per day which will usually increase to a dosage of between 6mg to 12mg.
- Reminyl is taken twice daily with food and is available in 4mg, 8mg and 12mg tablets. The recommended starting dose is 8mg to be taken daily for at least four weeks.

What questions should you ask your doctor?

- What are the potential benefits of taking these drugs?
- How long will it be before I see a result?
- How often do these drugs need to be taken?
- What should I do if a dose is missed?
- If there are side effects should the drug be stopped immediately?
- What happens if the drug is stopped suddenly?
- What other treatments (prescription and over-the-counter) might interact with these drugs?
- Can alcohol be consumed while taking the drug?
- How might these drugs affect other medical conditions?
- What changes in health should be reported immediately?
- How often will visits to the clinic/surgery be needed?
- Can someone with Alzheimer's disease living in a residential or nursing home take these drugs?

- Are there any costs associated with taking these drugs?
- Why is one drug prescribed rather than another?
- If one drug proves ineffective can another drug be tried?

Notes on drugs

Aricept (donepezil hydrochloride), produced by Eisai and co-marketed with Pfizer, was the first drug to be licensed in the UK specifically for Alzheimer's disease.

Exelon (rivastigmine), produced by Novartis Pharmaceuticals, was the second drug licensed in the UK specifically for Alzheimer's disease.

Reminyl (galantamine) was co-developed by Shire Pharmaceuticals and the Janssen Research Foundation. Originally derived from the bulbs of snowdrops and narcissi, Reminyl was the third drug licensed in the UK specifically for Alzheimer's disease.

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