Alzheimer's disease

Practical advice for management in general practice

New drug therapies have changed the way in which Alzheimer's disease is treated, but patients still require regular symptom review, guidance on practical and legal issues, and referral to community support services. GPs play a key role in each aspect of successful management.

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Alzheimer's disease accounts for approximately 60% of dementia in Australia. Memory loss is the cardinal feature, but there may also be impairment of cognitive and executive function, as well as changes in behaviour, personality and mood (see Table 1). Certain neuropathological changes of Alzheimer's disease are now well recognised (see Figures 1 to 3).

Management should be aimed at improving or stabilising the decline of cognition, function in daily activities, behaviour and mood, with the goals of improving quality of life and reducing the burden for the patient, family and caregiver.

Drug treatments for Alzheimer's disease

The availability of new drug treatments for Alzheimer's disease has increased the importance of making an early and accurate diagnosis (see Table 2).

Cholinesterase inhibitors are the only drugs currently marketed as symptomatic therapy for Alzheimer's disease. These drugs work by preventing the breakdown of acetylcholine in the synapse, thereby improving cholinergic neurotransmission. Acetylcholine has an important role in memory function;

IN SUMMARY

- **Cholinesterase inhibitors are indicated for symptomatic treatment of cognition and behaviour in mild to moderate dementia of Alzheimer's type.**
- **To date, no drugs have been proven to halt or slow underlying disease progression in Alzheimer's disease.**
- **In comparison to tacrine (Cognex), donepezil (Aricept) is devoid of hepatotoxicity, has improved gastrointestinal tolerance, and simplified compliance, prescribing and monitoring.**
- **Depression can coexist with Alzheimer's disease and should be treated appropriately.**
- **Regular assessment of the presence and impact of behavioural and psychological symptoms associated with Alzheimer's disease is important in management.**
- **Pharmacological treatment for behavioural symptoms should be reserved for drug-responsive symptoms that are causing at least moderate distress to the patient or caregivers.**
- **Counselling should include early attention to practical and legal issues and, in particular, discussion of the impact of Alzheimer's disease on driving safety.**
- **The Alzheimer's Association provides a range of support and educational services for patients in every State and Territory. GPs and patients can contact the Association on the national toll-free HelpLine, 1800 639 331.**

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the major deficiency in Alzheimer's disease is that of acetylcholine.

What drugs are available?

The first cholinesterase inhibitor developed was tacrine (Cognex), which is little used as a result of problems with hepatotoxicity and poor gastrointestinal tolerance. A number of second generation drugs with improved side effect profiles are now available or under development. The first of these, donepezil (Aricept), was marketed in Australia 12 months ago and is currently the drug of choice because it has greatly improved tolerance.

Donepezil is available on private prescription at considerable cost (applications for PBS and RPBS subsidy have not been approved to date). Other cholinergic drugs are likely to follow onto the market in the future.

Approval for rivastigmine has been submitted to the TGA, and it may be available later in 2000. Galantamine is in the marketing pipeline. Rivastigmine and galantamine appear to have similar efficacy, although there are no direct comparative studies.

Why should cholinesterase inhibitors be used?

Treatment with the cholinesterase inhibitors may improve symptoms or stabilise decline, resulting in a gain of six to 12 months, but cannot halt or reverse progression of the disease.

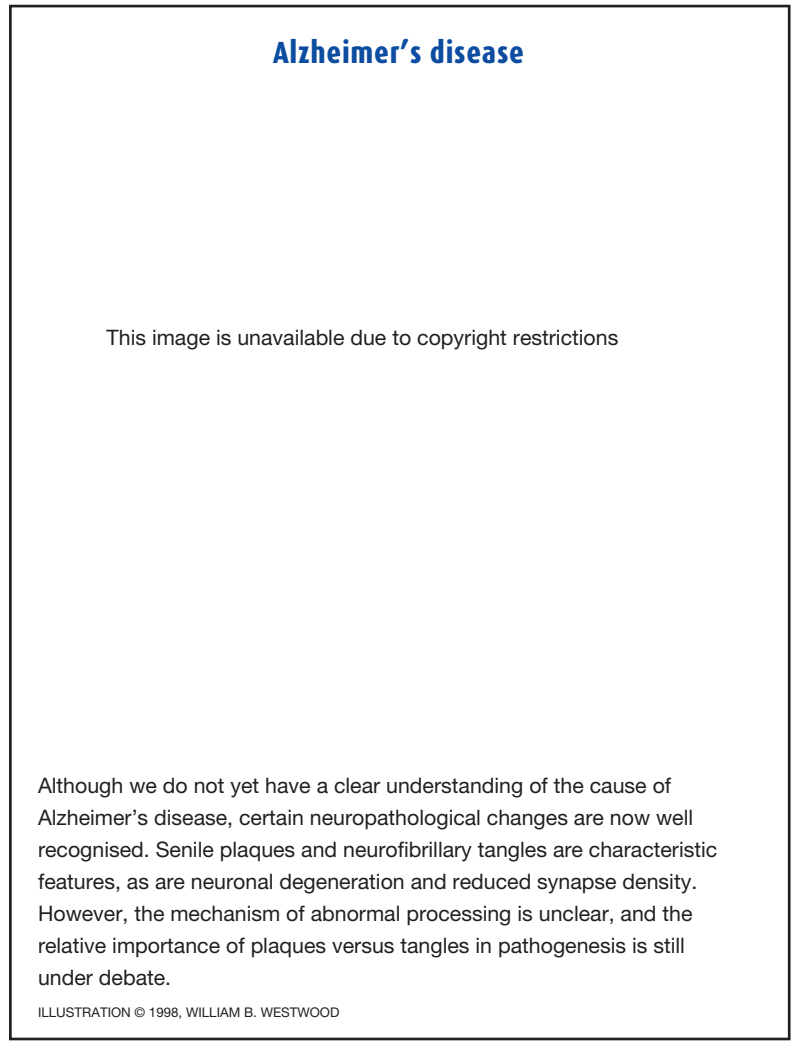
It has been suggested that cholinesterase inhibitors slow the progression by altering the rate of cognitive decline, but this has not been proven. Two large international studies have shown a modest benefit in 60 to 70% of patients treated with cholinesterase inhibitors. About 20% of these patients demonstrate a more significant response, but the characteristics of this subgroup are unknown.[2,3]

The benefits of treatment with cholinesterase inhibitors may be apparent in various areas, including:

- concentration and alertness
- memory
- speech
- problem-solving ability
- daily functional activities, particularly initiation of tasks.

A number of caregivers report improvement in mood and behaviour for patients with

Alzheimer's disease



Although we do not yet have a clear understanding of the cause of Alzheimer's disease, certain neuropathological changes are now well recognised. Senile plaques and neurofibrillary tangles are characteristic features, as are neuronal degeneration and reduced synapse density. However, the mechanism of abnormal processing is unclear, and the relative importance of plaques versus tangles in pathogenesis is still under debate.

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Table 1. Diagnostic features of Alzheimer's disease

- Acquired decline in cognitive function of insidious and progressive nature
- Memory loss (a cardinal feature)
- Impairment of at least one of the following:
  - language
  - perception
  - praxis
  - problem solving, planning, organisation, judgement, insight or abstract thought
- Symptoms sufficient to impact on daily functioning

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Table 2. Advantages of early recognition of Alzheimer's disease[1]

- Early treatment with recently developed cognitive enhancing drugs
- Opportunities for patients and families to adapt to education and counselling aids
- Reduced carer stress
- Initiation of community support
- Attention to other medical issues (such as drug compliance and home safety)
- Delay in institutionalisation
- Opportunities for planning lifestyle and legal issues (such as a will, enduring power of attorney and power of guardianship)
- Supervision of driving and early detection of driving incapacity
- Involvement in research (epidemiological research and drug treatment trials)

Alzheimer's disease treated with cholinesterase inhibitors, which can help in management and improve quality of life.

Who should be treated?

Donepezil is indicated for patients with Alzheimer's disease of mild to moderate severity. There is no indication for patients with age-associated memory loss alone.

Trials are underway to test potential benefit in vascular dementia, diffuse Lewy body dementia and more severely impaired Alzheimer's disease. The Mini Mental State Examination can be used as a rough guide to disease severity (see the box on page 23).

When should treatment be commenced?

After a diagnosis of Alzheimer's disease is established, treatment can be commenced as soon as benefit is sought (see the flowchart on page 26).

Anecdotal experience suggests that quality of life can be improved with treatment at the early stages of Alzheimer's disease when cognitive impairment is mild and behavioural problems are less common.

Some patients with limited financial resources may delay the commencement of treatment until symptoms are more disabling.

How is donepezil prescribed?

Treatment with donepezil should begin at a dose of 5 mg daily (clinically effective dose) for the first four to six weeks, and can be increased to 10 mg daily if the lower dose is well tolerated. Women of low body weight are more likely to be intolerant of the higher dose.

The medication should be taken at night in order to reduce the impact of any gastrointestinal side effects; however, some patients with insomnia find that morning administration reduces this problem. Donepezil is taken with a glass of liquid, with or without food.

No dose modification is required for patients who have hepatic or renal dysfunction, and drug interactions have not been demonstrated other than the expected potentiation of other cholinomimetic drugs. Drugs with anticholinergic action will oppose the therapeutic effect of cholinesterase inhibitors and are contraindicated in patients with cognitive impairment. There is no requirement

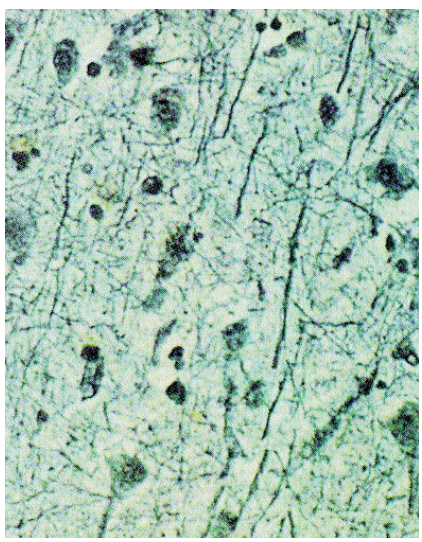

Figure 1. Histological appearance of normal brain.

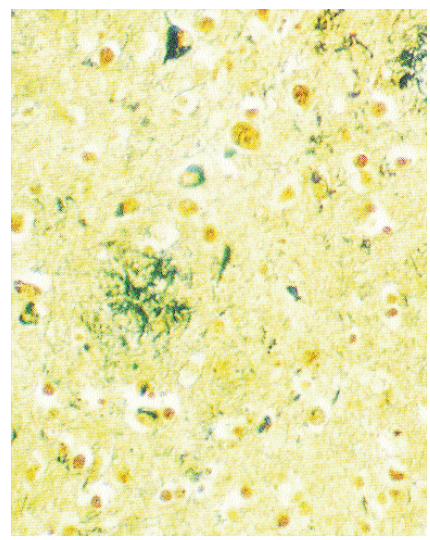

Figure 2. Senile plaques in Alzheimer's disease.

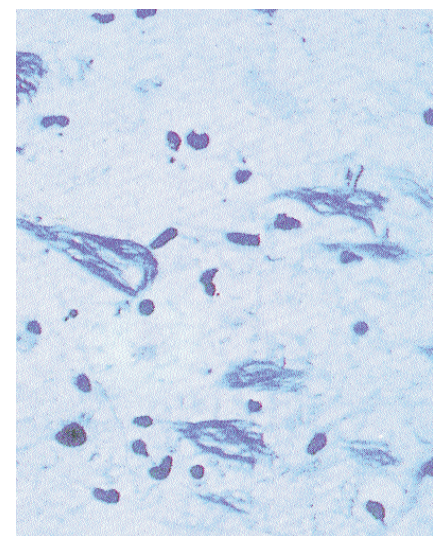

Figure 3. Neurofibrillary tangles in Alzheimer's disease.

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The Mini Mental State Examination*

The Mini Mental State Examination is commonly used to assess the severity of cognitive impairment in patients with Alzheimer's disease.

Instructions

Before you begin, get the patient's permission to ask some questions. This will help to avoid catastrophic reactions. Provide any hearing or visual aids that the patient needs. You will also need a watch, pencil and some paper.

Do not engage in conversation, give hints or physical clues (such as head shaking). If a question is answered incorrectly, accept the patient's answer and do not ask the question again. The test takes approximately 10 minutes to complete.

Scoring

The test is scored out of 30. A score of 18 to 26 suggests mild dementia; a score of 10 to 17 suggests moderate dementia; and a score of less than 10 suggests severe dementia. However, the score is a guide only, and requires clinical judgement. Scores are influenced by factors such as language, culture, educational background, and visual or hearing impairment.

Questions	Score
Orientation	
1. Ask the following questions about time. Score 1 point for each correct response.	
a. What year is this?	/1
b. What season is this?	/1
c. What is today's date?	/1
d. What day of the week is it?	/1
e. What month is it?	/1
2. Ask the following questions about location. Score 1 point for each correct response.	
a. What State/Territory are we in?	/1
b. What country are we in?	/1
c. What town or city are we in?	/1
d. In clinic: What is the name of this hospital (or building)? At home: What is the street address of this house?	/1
e. In clinic: What floor of the building are we on? At home: What room are we in?	/1
Registration	
3. Tell the patient that you are going to name three objects, and that you will then ask the patient to name them. The objects can be an apple, table and penny. Score 1 point for each correct reply on the first attempt only. Explain that you want the patient to remember the three objects because you are going to ask him or her to repeat them again in a few minutes. If the patient does not repeat all three objects, repeat up to six times until they are learned (for the recall test in Question 5).	/3
Attention	
4. Ask the patient to subtract 7 from 100, then subtract 7 from the result, and so on, for 5 subtractions. Score 1 point for each correct answer. Alternatively, ask the patient to spell the word 'world' backwards. Score 1 point for each correct letter.	/5

Recall	Score
5. Ask the patient to name the three objects that you asked him or her to remember earlier (in Question 3). Score 1 point for each correct response, regardless of order, on the first attempt only.	/3
Language	
6. Show the patient a pencil and a watch. Ask the patient to name the two objects. Score 1 point for each correct name.	/2
7. Ask the patient to repeat the following sentence after you: 'No ifs, ands or buts'. Score 1 point for a completely correct repetition.	/1
8. Ask if the patient is left or right-handed. Then ask the patient to follow a three-stage command, including the other hand in the instruction. For a right-handed patient, say 'Take a paper in your left hand, fold it in half and put it on the floor'. Score 1 point for each part correctly executed on the first attempt only.	/3
9. Hand the patient a sheet of paper with 'close your eyes' written on it. Tell the patient to read the message and then follow the instruction. Score 1 point if the patient closes the eyes.	/1
10. Hand the patient a pencil and paper and ask him or her to write any sentence on the paper. Score 1 point for a sentence that makes sense, ignoring spelling errors.	/1
11. Give the patient a paper, pencil and eraser. Show the patient a design of two intersecting pentagons, and ask the patient to copy it. Score 1 point for a correctly copied design (i.e. a four-sided figure between two five-sided figures). 	/1
TOTAL SCORE	/30

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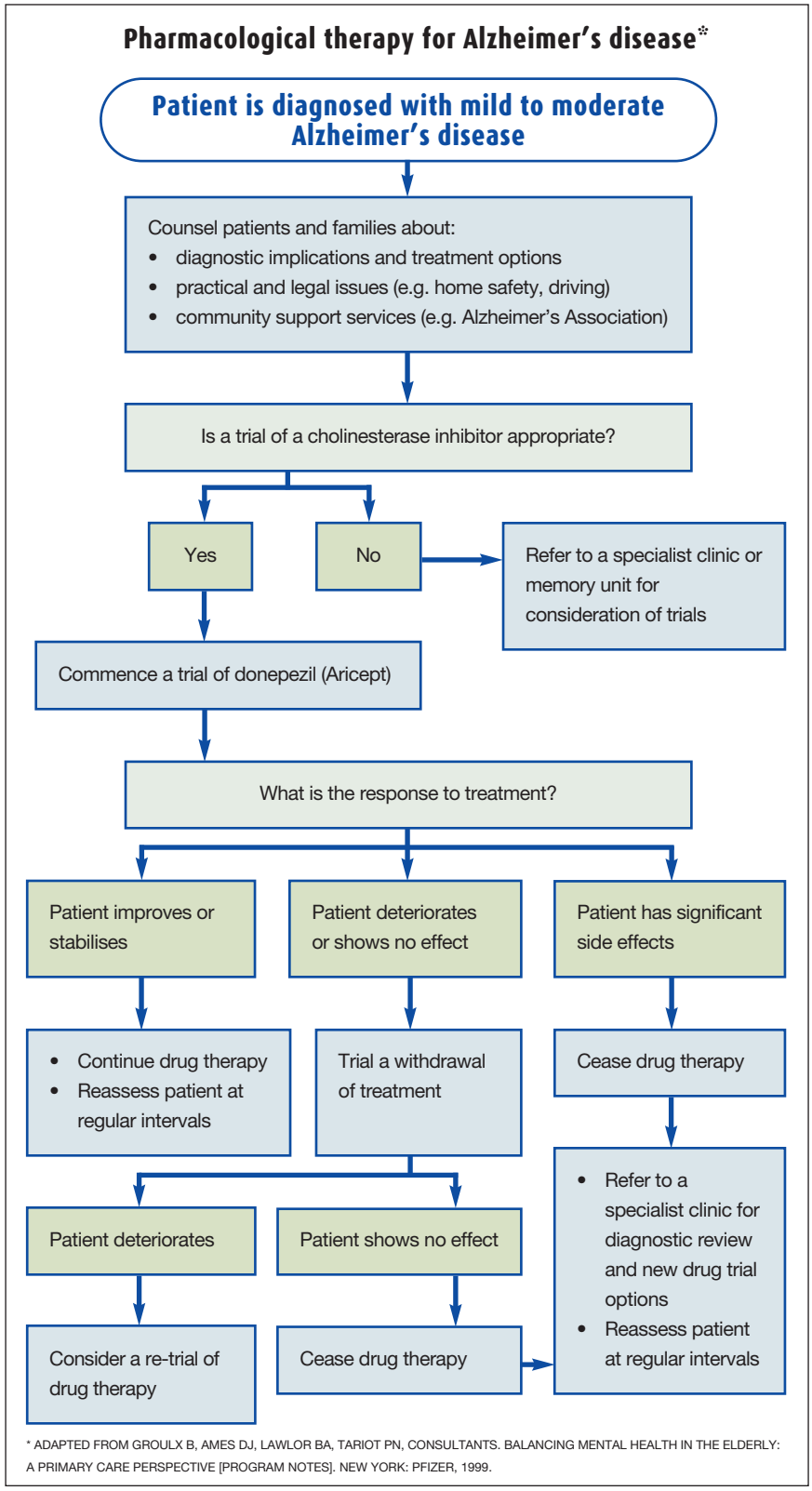

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for biochemical monitoring. Patients should be reviewed at one, three and six months to assess efficacy and side effects of treatment.

What are the side effects of donepezil?

Donepezil is well tolerated by most patients. The incidence of expected cholinergic side effects is low; nausea and diarrhoea are the most common problems.

Other nonspecific side effects can include headache, fatigue, insomnia, dizziness and muscle cramps. Occasional patients develop agitation, hallucinations or unpleasant dreams which reverse on cessation of the drug.

How long should treatment be continued?

Benefit appears to be maintained while therapy continues, but earlier studies suggest loss of effect within six weeks if treatment is discontinued.[2,3]

Open label data are now available for patients treated for more than four years, but published double-blind placebo-controlled scientific studies have not exceeded six months' duration. Data from the recently completed 12-month Scandinavian trial with donepezil have been presented, and show positive efficacy over this period.[5]

If treatment benefit is doubted, an effective clinical test is a withdrawal trial – treatment can be reinstituted if deterioration follows drug withdrawal.

Assessment of the treatment effect should include discussion with the patient and the caregiver or informant, as well as an objective test of cognitive function – the Mini Mental State Examination is a useful brief instrument (see the box on page 23).

What about other putative cognitive enhancers?

A number of drugs are reputed to have cognitive enhancing effects.

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Ginkgo biloba

Ginkgo biloba, a derivative of the leaf of the Chinese maidenhair plant, is sold in health food shops. There are a couple of well conducted scientific studies that have supported a very small positive effect on cognitive function.[6-8] The active ingredient tested (EGb716) is contained in varying quantities in differing preparations of this drug.

Antioxidants

Antioxidants have long been postulated as effective in a number of degenerative diseases associated with ageing. There are no studies showing a benefit on cognitive function, but one large study suggested a positive effect of vitamin E (1,000 IU twice daily) or selegeline on the rates of death, time to institutionalisation, and loss of basic daily living activities.[9]

Folate

Recent studies in several sites have shown a correlation between Alzheimer's disease, high serum homocysteine levels and low serum folate. [10,11]

As yet, there is no evidence that high homocysteine or low folate is causative in Alzheimer's disease, as opposed to a consequence or association of Alzheimer's disease. No treatment studies have been conducted, nor can treatment implications be drawn from the evidence to date. Further research in this area may lead to promising therapeutic advances.

Other agents

A number of other agents are being tested in large international studies for potential benefits on disease progression. These include anti-inflammatory drugs, oestrogens, lazabemide (monoamine oxidase B inhibitor), metabolic enhancers and neurotrophic agents.

The results of the lazabemide study which were presented at the 1999 International Psychogeriatric Association meeting in Vancouver showed a statistically significant delay in deterioration on neuropsychology and daily activity scale. Unfortunately, this drug has recently been withdrawn from development following a small number of cases of hepatotoxicity.

Practical and legal issues

When counselling patients with Alzheimer's disease and their families, a number of other important areas should be covered in addition to the diagnosis and treatment options.

A family conference can be organised to discuss relevant issues at the time of diagnosis, including:

- the nature and implications of Alzheimer's disease
- treatment options
- long term planning, including legal issues
- guidance on practical management, including community support services.

Testamentary capacity

Patients with an early diagnosis of Alzheimer's disease who retain testamentary capacity can organise appropriate provisions for a will, enduring power of attorney (management of finances and assets), enduring power of guardianship (management of treatment and lifestyle decisions) and advance directives.

It is important that these documents be brought to the attention of patients at the time of the diagnosis, before legal capacity is lost and guardianship board involvement is required.

Capacity is a legal concept and is decision-specific, requiring assessment of the ability to understand the relevant information and appreciate the consequences of decisions.[12]

Driving

Driving is a difficult issue that faces all GPs at times. As practitioners involved in the role of caring and support, the legal requirement to report patients whose physical or mental impairment is likely to affect driving safety often produces a conflict of interest.

There is an opportunity to perform brief cognitive screening when medical certification of fitness to drive at periodic intervals is a requirement in older patients. Objective evidence of possible cognitive impairment can be followed with more detailed assessment and diagnosis.

When a diagnosis of Alzheimer's disease is established, it is important to discuss driving ability with the patient and family.

In a large number of patients, it is effective to explain the many ways in which Alzheimer's disease can affect driving performance, and to encourage self-restriction and appropriate voluntary licence relinquishment.

It is useful to discuss this issue at an early stage, when insight is better maintained. This will allow time for patients to accept the loss of driving and to plan alternative arrangements.

Studies have suggested that patients with moderate and severe dementia are clearly unsafe on the road.[13] However, the situation is very variable in mild dementia, and many patients are safe drivers in the early stages of Alzheimer's disease.

Mandatory licence suspension on diagnosis (which is not required in Australia) seems to be unnecessarily harsh, but there no clear guidelines on how to assess risk in the clinical setting. In situations of doubt or a lack of patient co-operation, an on-road driving assessment, preferably conducted by a skilled assessor (such as an occupational therapist), can provide objective evidence and relieve the doctor of having to take the punitive role.

Activities of daily living

Practical advice on maximising function may help on a wide range of issues, including:

- aids for memory and orientation
- drug compliance

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- home safety
- communication hints
- suitable diversional activities
- appropriate structuring of the home environment.

In the more advanced stages of the disease, advice about nutrition and the management of continence and personal care may be of help.[14]

Superimposed problems

From a medical perspective, it is important to consider, detect and treat any superimposed medical problems or drug-induced iatrogenic problems that may be compounding disability.

This is particularly relevant if there has been recent unexplained cognitive decline, superimposed delirium or new behavioural problems.

A proactive approach of scheduling routine regular reviews with the patient and family at intervals of three to six months will allow problems to be detected at an early stage and preventive strategies to be instituted.

Carer stress

The carer is the second victim in Alzheimer's disease, and the stress associated with the caregiving role can result in medical and psychological morbidity associated with increased use of health services.

Appropriate education, counselling and support together with adequate provision of respite services can improve carer health and delay the requirement for residential care.

Referral to the Alzheimer's Association lends support to the GP's input. GPs or patients can contact the Alzheimer's Association in their State or Territory on the national toll-free HelpLine, 1800 639 331.

Depression and Alzheimer's disease

Depression and Alzheimer's disease can present with similar symptoms and can be difficult to differentiate clinically. Symptoms include:

- memory loss
- poor concentration
- reduced interest and initiation of activities
- changes in psychomotor activity
- sleep disturbance
- fatigue
- changes in eating habits or weight.

In pseudodementia or 'reversible dementia', cognitive impairment improves or reverses with the successful treatment of depression. If in doubt, a trial of antidepressant therapy is indicated. Late onset depression associated with cognitive impairment is associated with a higher rate of dementia (vascular dementia and Alzheimer's disease).

Depression is also a common concomitant diagnosis in patients with Alzheimer's disease, more commonly in the early stages of dementia. Symptoms of depression, which are present in up to 40% of patients with Alzheimer's disease, are generally under-recognised and undertreated.

Appropriate treatment should be instituted, including supportive counselling and, if necessary, antidepressant drug therapy. The choice of pharmacological agent should take into account the side effect profile of different drugs: drugs with anticholinergic effect (such as tricyclic antidepressants) can increase confusion and are best avoided.

The selective serotonin reuptake inhibitors (SSRIs) with relatively short half-lives and minimal anticholinergic, adrenergic and histaminic side effects are a good choice.

Managing psychological and behavioural symptoms

Changes in personality and behaviour are commonly associated with Alzheimer's disease, often becoming significant in the moderate and severe stages of dementia. There is great individual variation in the occurrence and severity of behavioural symptoms, but they are often extremely disruptive to patients and caregivers in both home and residential care settings, resulting in reduced quality of life and increased costs of care.

The management of psychological and behavioural symptoms in Alzheimer's disease is presented in the flowchart on page 31.

Nonpharmacological approaches

A thorough assessment should include identification of the specific problem behaviour, documentation of relevant antecedents and consequences, and a careful search for any medical illness, physical symptoms or iatrogenic factors (drug side effects or interactions) that may be contributing.

Nonpharmacological approaches (including environmental interventions) should be tried before resorting to drug therapy.

Pharmacological therapy

Pharmacological therapy should be reserved for drug-responsive symptoms of at least moderate severity that are disturbing to the patient or caregivers.

Antipsychotic medication is most effective in the treatment of psychotic symptoms (delusions and hallucinations), agitation and aggression.

When choosing a therapeutic agent, consideration should be given to the side effect profile of individual drugs. In general, elderly patients with dementia are more sensitive to centrally acting drugs, and the dosages of medication required are significantly lower.

It is important to begin treatment with a low dose and to increase the dose slowly. Regular review of both efficacy and any potential adverse effects is important. In general, if antipsychotic treatment is required, use of a potent antipsychotic with minimal anticholinergic action, in low dose, is the preferred option (e.g. haloperidol [Serenace], 0.5 mg once or twice daily).

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Patients with diffuse Lewy body dementia (an increasingly recognised form of dementia) often respond very poorly to antipsychotics, deteriorating in both mobility and cognition. It is preferable to avoid the use of neuroleptics in this group.

The newer antipsychotic drugs, such as risperidone (Risperdal) and olanzapine (Zyprexa), appear to be at least as effective as conventional neuroleptics but with fewer undesirable side effects, particularly on the extrapyramidal system. These agents are used routinely in other countries, but are not currently authorised in Australia for behaviour management in dementia.

Specialist clinics and memory units

The availability of new drug treatments for Alzheimer's disease increases the importance of early and accurate diagnosis.

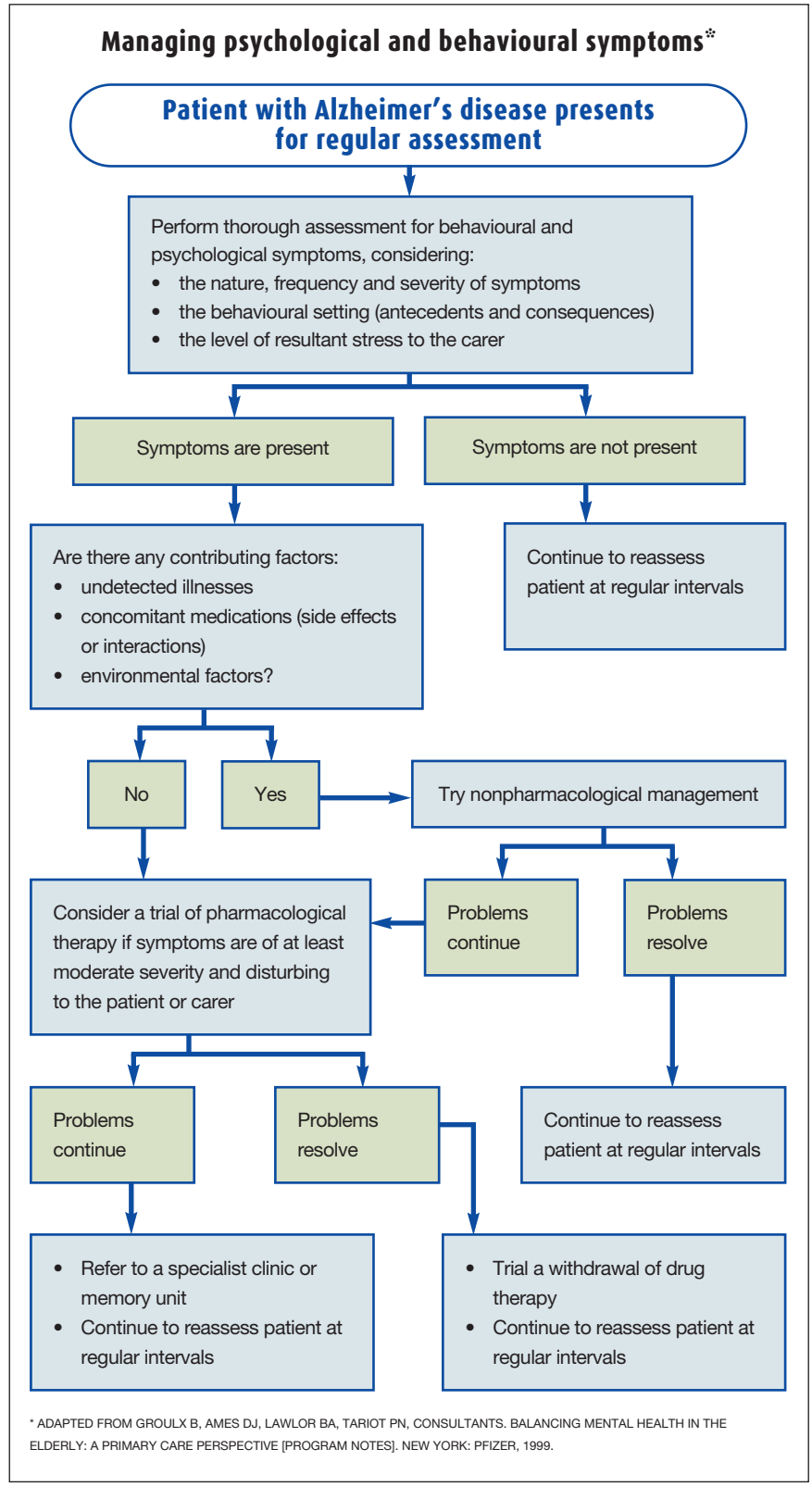
Distinguishing early Alzheimer's disease from age-associated memory loss can be difficult, and assessment at a specialist clinic with detailed neuropsychological testing can be helpful.

Dementias that can easily be mistaken for Alzheimer's disease include:

- frontal dementia
- diffuse Lewy body dementia (thought to account for 20 or 30% of previous cases)
- focal atrophy syndromes.

Referral to a specialist or memory unit may also be required when:

- there is diagnostic uncertainty – for example, an atypical or complicated presentation or disease course, early or mild impairment, very high or low premorbid education or intellect, or disease onset at young age (less than 65 years)
- the disease course is unexpected or rapidly deteriorating
- management of resistant behavioural or psychological symptoms is required



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- the patient or family requests a specialist opinion.

Specialists and memory units can provide advice about testamentary capacity and driving ability, as well as new drug treatments. They also have an interest in clinical drug trials.

Can Alzheimer's disease be prevented?

Unfortunately, there is no current evidence to support the use of any pharmacological agent in the role of prevention, but research is underway in the area. A number of studies are being conducted worldwide in patients with memory loss or mild cognitive impairment to test agents that may delay the onset of Alzheimer's disease.

Drugs under investigation for disease prevention include cholinesterase inhibitors, anti-inflammatory agents, antioxidants (including vitamin E) and oestrogens (in women). No such studies are currently being conducted in Australia.

Conclusion

General practitioners are in a unique position to detect and diagnose Alzheimer's disease. Regular medical review is necessary in this chronic, progressive disease to assess cognition, functional performance in daily living activities, and behavioural and psychological symptoms associated with Alzheimer's disease.

Ongoing medical management should include careful detection and treatment of intercurrent illness, and attention to drug compliance, side effects and interactions.

The burden may be eased and residential care may be delayed with continuing education and counselling support, monitoring of carer stress and referral to community support services.

Knowledge of new drug therapies and research directions is increasingly relevant. MT

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Further reading

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