
Progress

— in Neurology and Psychiatry —

Case Notes

**Galantamine once daily
(Reminyl XL) in the management
of mild to moderate Alzheimer's
disease**

This supplement is supported by an educational grant from
Shire Pharmaceuticals

Prescribing information can be found on page 7

Introduction

Dr Roger Bullock

Alzheimer's disease (AD) is an increasingly common illness, predominantly of the elderly, which imposes a heavy burden on statutory services, individuals and their carers. The prevalence is estimated at around 5000 per 100 000 over the age of 65 years,¹ but these figures approximately double with every 5.1 years of age.² Treatments for mild to moderate AD were first introduced in 1997. Conservative estimates of the annual cost to the NHS and social care services of AD reach about £5 billion,³ quadrupled if the informal costs of caregiving are also included.⁴ This is why attempts to delay the progress of AD by early intervention are important, as extrapolation from incidence data would suggest that a 2-year delay of symptoms could reduce the prevalence of dementia (where most costs are incurred) by as much as 20 per cent after 10 years.⁵

Acetylcholinesterase inhibitors are proven to offer symptomatic

relief across a range of symptoms in AD, including cognition, function and behaviour.^{6,7} These can be measured using simple scales (see Table 1) such as the Mini-Mental State Examination (MMSE),⁸ the Disability Assessment for Dementia scale (DAD)⁹ and the Neuropsychiatric Inventory (NPI).¹⁰ These provide a lot of information, but perhaps asking the patient and carer what they hope to achieve and measuring to what extent this occurs is the measurement that fits best with clinical practice. One scale that uses this type of approach is Goal Attainment Scaling (GAS).¹¹ This approach is more relevant to the individual patient, as responses to any treatment are individual and idiosyncratic, which means that some scales may not capture true clinical benefit. The overall goal for most patients and their carers is for the patient to be able to remain independent, coping with

daily activities of living in their own homes for as long as is practical. The plea from most patients and carers is 'Please help keep us together'.

The use of acetylcholinesterase inhibitors has increased since their introduction. With broadly similar clinical profiles, choices have sometimes been made based on their pharmacological differences, but also primarily on ease of use. Galantamine has repeatedly demonstrated efficacy across all the domains of AD, and has been shown to maintain cognitive function at or above baseline for at least 12 months.^{7,17,18} Its tolerability has been consistently good, but until June 2005, it was only available as a twice daily preparation. A once daily prolonged release formulation (Reminyl XL) is now available and may be helpful to those who had found managing twice daily treatments problematic.

Scale abbreviation	Full title	Function
MMSE ⁸ DAD ⁹ NPI ¹⁰ GAS ¹¹	Mini-Mental State Examination Disability Assessment for Dementia Neuropsychiatric Inventory Goal Attainment Scaling	<ul style="list-style-type: none"> Assess cognitive aspects of mental function Assess functional disability in dementia Assess psychopathology in dementia Measure the attainment of individualised, clinically important patient goals and outcomes
ADAS-Cog ¹²	Alzheimer's Disease Assessment Scale – Cognitive subpart	<ul style="list-style-type: none"> Screen patients with probable AD and measure cognitive function during drug therapy
CGIC ¹³	Clinical Global Impression of Change	<ul style="list-style-type: none"> Assess global severity of illness and clinical change over time
CIBIC-Plus ¹⁴	Clinical Interview-Based Impression of Change, plus carer interview	<ul style="list-style-type: none"> Measure the change in cognitive, behavioural functioning and activities of daily living
BEHAVE-AD ¹⁵	Behavioural pathology in Alzheimer's Disease Scale	<ul style="list-style-type: none"> Measure changes in behavioural symptoms and outcomes of treatments
ADCS-ADL ¹⁶	Alzheimer's Disease Cooperative Study/Activities of Daily Living	<ul style="list-style-type: none"> Measure cognitive and functional deficits in people with AD

Table 1. Rating scales commonly used to quantify symptom scores in Alzheimer's disease

First clinical vignette

new patient starting on a once daily therapy

Professor Stephen Curran

Mr J was a 74 year old man who was referred by social services and was initially seen at home by the community mental health team. An initial assessment at home revealed mild to moderate cognitive impairment and an MMSE score of 21. Mr J lives alone and his activities of daily living were impaired. In particular, his personal hygiene was poor and his daughter was having difficulty persuading him to accept help; he was therefore referred to and reviewed in the local memory service. He had a number of physical health problems including 'back ache' but was otherwise physically well. There was no past history of psychiatric illness and no relevant family history. His wife died several years ago and he has one daughter who is his main carer, but she is only able to visit once daily (mornings) because of work. He is supported by social services during the rest of the day and attends a local day centre twice weekly. After a full assessment in the memory service including routine laboratory investigations and a CT scan he was started on galantamine prolonged release 8mg each morning. This was subsequently increased to 24mg daily. In our opinion, galantamine prolonged release

was chosen partly because his daughter was only able to supervise his medication once daily in the morning, but also because of its good tolerability in the setting of physical illness and in patients taking other medications. The medication has been well tolerated and the clinical response has been very good. Cognitive function has improved (26 on the MMSE) and his activities of daily living, and particularly his personal hygiene, have also improved. His daughter has noted these improvements. Once daily treatment in the morning has been very helpful to his daughter. She calls in to see her father before going to work and supervises his medication but is not able to return in the evening because of family pressures. Once daily galantamine was easy to use and there were no interactions with Mr J's other medication (paracetamol 1mg twice daily) or exacerbation of his physical health. Treatment was delayed while we waited for a CT scan. The CT scan did not make any significant difference to either the diagnosis or treatment, and the need for a CT scan in patients with uncomplicated mild to moderate Alzheimer's disease is worth questioning if it is likely to lead to a significant delay in starting treatment.

Second clinical vignette

switching to galantamine once daily

Dr Sean Lennon

Mrs B was aged 82 years when first referred to the memory clinic. She was found to have a moderate degree of cognitive impairment due to Alzheimer's disease. She was reluctant to talk about symptoms or difficulties at home and needed encouragement to take medication. We discussed the diagnosis and agreed that Mr and Mrs B would attend a post-diagnostic counselling group, and that she would

receive treatment with an acetylcholinesterase inhibitor. In our service, treatment is managed through a shared care protocol with the person's own GP. Using this protocol, Mrs B was started on rivastigmine 1.5mg twice daily. The dose was increased to 3mg twice daily after 28 days. Unfortunately, she experienced vomiting and abdominal pain within a week of the dose being

Second clinical vignette (continued)

increased. Mrs B persisted with the medication but, even after a week, there was no improvement in the symptoms and her husband contacted our service for advice. The rivastigmine was stopped immediately with complete resolution of the vomiting and discomfort within a few days. A week later she was started on galantamine prolonged release 8mg once daily. She and her husband were given advice on possible side-effects. She was reviewed after a month and had experienced no side-effects. The dose was therefore increased, according to our protocol, to galantamine prolonged release 16mg once daily. Within 2 weeks of the increase her mood changed; she was described as being more irritable and emotionally upset. We concluded that she was experiencing an adverse effect of galantamine. The dose was reduced to 8mg once daily with a rapid improvement

in irritability. After a further 4 weeks the dose was increased again, and she has now tolerated galantamine prolonged release 16mg once daily without any side-effects. Her husband has commented that the visual hallucinations have begun to appear less often. Mrs B suffered side-effects typical of acetylcholinesterase inhibitors from both rivastigmine and galantamine. However, the side-effects were different for each drug. The management of her side-effects using a slow titration of galantamine prolonged release has been successful in achieving tolerance of the medication. Although we routinely provide written information about acetylcholinesterase inhibitors and possible side-effects, in Mrs B's case, her husband had been reluctant to tell us about side-effects because he feared that no alternative would be available.

Third clinical vignette

switching to an alternative once daily therapy

Professor Stephen Curran

Mrs F was a 69 year old lady referred to the memory service by her GP. She had had problems with her memory for approximately 2 years, especially her short-term memory, and this had been getting gradually worse. On presentation she had an MMSE score of 22. She needed some assistance with her activities of daily living, including dressing and personal hygiene, but she was able to make a cup of tea safely and prepare a sandwich. Her social skills remained very good. She was physically well and there was no past history of psychiatric illness. She has lived alone since her husband's death some years ago but is supported by two daughters. They both work and take it in turns to visit on alternate days, but are only able to visit once daily because of work and family pressures. After a full assessment in the memory service a diagnosis of mild dementia of the Alzheimer's type

was made. Mrs F also receives input from a professional carer at lunchtimes and early evenings. After looking at information on the internet the family asked if Mrs F could be started on donepezil 5mg at night, and this was agreed. Initial response to treatment was poor, but after 4 weeks the dose was increased to 10mg and cognitive function improved to 25 on the MMSE. However, Mrs F developed significant and persistent muscle cramps which kept her awake at night, and after a further 4 weeks it was decided to discontinue donepezil and start galantamine prolonged release 8mg daily. The switch over was uneventful and the muscle cramps resolved after several days. In addition, cognitive function was maintained and after 1 month the galantamine prolonged release was increased to 16mg daily. We are planning to increase this to 24mg daily in the near future.

Commentary

Dr Sean Lennon

Acetylcholinesterase inhibitors have similar primary modes of action. However, they differ in tolerability in unpredictable ways. For this reason, it is appropriate to switch between acetylcholinesterase inhibitors if a patient experiences an adverse effect from one of these drugs.¹⁹

When changing between acetylcholinesterase inhibitors it may be appropriate to taper the first drug until discontinued completely. If, however, the side-effects have emerged soon after starting the medication, tapering the dose is unnecessary. If the acetylcholinesterase inhibitor has been given for a period of time then it is always important to allow a wash-out period to avoid concomitant prescription of two drugs from this class of medication. Based on the

Learning points

- 1 Provide patients and their carers with written information about their medications including advice about adverse effects
- 2 When switching between acetylcholinesterase inhibitors after long-term use, the dose of the first drug should be tapered and a drug-free period of 5 half-lives is suggested
- 3 Slowing the upward titration of dose of an acetylcholinesterase inhibitor may reduce the risk of adverse effects
- 4 Galantamine prolonged release once daily is well tolerated and is easy to use

evidence, it has been suggested that an adequate wash-out period is 5 half-lives of the original drug.²⁰

When switching medications after adverse effects, it is prudent to be prepared to increase the dose cautiously.

Galantamine prolonged release represents an alternative when switching from another acetylcholinesterase inhibitor for

patients who experience side-effects or do not improve with other drugs. Although it is a once daily medication, it does not have a long half-life and so, if an adverse effect recurs, it should settle quickly on discontinuation of the drug. The drug is easy to use. Switching to galantamine is straightforward both clinically and from a practical perspective.

Specialist Nurse Perspective

Mr Sean Page

The aim of effective pharmacotherapy is to enhance the quality of life for people affected by dementia. Yet patient treatment regimes can fail to recognise individual preferences, or can be so complex that they lead to non-compliance among people with dementia.

The situation can be improved by recognising and valuing the important role that partners of those affected by dementia can play in defining a realistic treatment plan. This

approach is underpinned by the belief that informed treatment choice balances a person's needs (including lifestyle and preferences), and the convenience, efficacy and tolerability of treatments available.

Efficacy, tolerability and convenience are significant factors that affect a patient's decision about the risks and benefits of continuing with treatment. Strong evidence of efficacy reassures patients that the treatment they are to undertake will be of benefit,

and, as an ideal treatment regime should not interrupt a patient's established routines, tolerability and convenience become important considerations.

If these factors are taken into account, concordance can be achieved and maintained over a sustained length of time. This allows time for treatment to be effective, and can lead to a period of stability for patients with dementia. A period of stability represents a therapeutic window through which a range of psychosocial

interventions, aimed at maximising potential and promoting coping mechanisms, can be delivered.

Effective pharmacotherapy creates this window of therapeutic

opportunity and, providing convenience and tolerance are achieved, keeps it open. Its significance, therefore – in terms of preservation of independent

functioning, reducing psychopathology, and improving quality of life for those affected by dementia – cannot be overstated.

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Prescribing Information

(Please refer to full Summaries of Product Characteristics [SmPCs] before prescribing)

Reminyl® XL 8mg, 16mg and 24mg prolonged release capsules; Reminyl 4mg, 8mg and 12mg Tablets and 4mg/ml Oral Solution

Presentation: Galantamine (as hydrobromide) provided as 8mg, 16mg and 24mg capsules; 4mg, 8mg and 12mg tablets; and 4mg/ml oral solution. **Uses:** Symptomatic treatment of mild to moderately severe Alzheimer's dementia (AD). **Dosage and administration:** Oral. Confirm diagnosis of probable mild to moderately severe AD prior to treatment. **Adults/Elderly:** Capsules to be taken once daily (o.d.). Tablets and oral solution to be taken twice daily (b.d.). Ensure adequate fluid intake during treatment. Capsules to be swallowed whole not chewed or crushed. **Starting dose:** 8mg/day (8mg o.d. or 4mg b.d.) for 4 weeks. **Initial maintenance dose:** 16mg/day (16mg o.d. or 8mg b.d.) for at least 4 weeks. **Maintenance dose:** 24mg/day (24mg o.d. or 12mg b.d.). Evaluate patients regularly – see SmPCs for full details. Consider reducing dose to 16mg/day if patient cannot tolerate higher dose or no increased benefit shown. **Moderate hepatic impairment:** reduce dose – see SmPCs. **Children:** Not recommended. **Contraindications:** Hypersensitivity, severe hepatic/severe renal impairment, patients with both significant renal and hepatic dysfunction. **Special Warnings and Precautions:** Benefit has not been demonstrated in other types of dementia or memory impairment (e.g. mild cognitive impairment) – see SmPCs. Cardiovascular conditions, predisposition or history of gastrointestinal ulcers, gastrointestinal obstruction/surgery, convulsions, cerebrovascular disease, severe asthma, obstructive pulmonary disease or active pulmonary infections (e.g. pneumonia), urinary obstruction, bladder surgery. **Capsules:** contain sucrose. **Tablets:** contain lactose and 12mg tablet also contains E110. **Oral solution:** contains methyl and propyl parahydroxybenzoate. **Interactions:** Other cholinomimetics, beta-blockers, digoxin, anaesthetics, CYP2D6 or CYP3A4 inhibitors. Also,

for capsules: certain calcium-channel blocking agents, amiodarone. **Pregnancy and Lactation:** Not recommended. **Undesirable Effects:** Very common (>1/10): Nausea, vomiting. Common (>1/100, <1/10): Rhinitis, urinary tract infections, anorexia, weight decrease, confusion, depression (very rarely with suicidality), insomnia, dizziness, somnolence, syncope, tremor, abdominal pain, diarrhoea, dyspepsia, asthenia, fatigue, fever, headache, malaise, fall, injury. Uncommon (>1/1,000, <1/100): Paraesthesia, tinnitus, atrial arrhythmia, myocardial infarction, myocardial ischaemia, palpitation, cerebrovascular disease, transient ischaemic attack, leg cramps. Rare (>1/10,000, <1/1,000): Dehydration (leading to renal insufficiency and renal failure), hypokalaemia, aggression, agitation, hallucinations, seizures, bradycardia (severe), rash. Very rare (<1/10,000): Worsening of Parkinsonism, AV block, hypotension, dysphagia, gastrointestinal bleeding, increased sweating. **Overdose:** General supportive measures. Atropine in severe cases. **Basic NHS price:** **Capsules:** 8mg x 28: £54.60; 16mg x 28: £68.32; 24mg x 28: £84.00. **Tablets:** 4mg x 56: £54.60; 8mg x 56: £68.32; 12mg x 56: £84.00. **Oral Solution:** 4mg/ml x 100ml: £120.00. **Legal category:** POM. **Product Licence numbers:** **Capsules:** PL 08557/0052-0054, **Tablets:** PL 08557/0039-0041 and **Oral Solution:** PL 08557/0042. **Product Licence holder:** Shire Pharmaceuticals Limited, Hampshire International Business Park, Chineham, Basingstoke, Hampshire, RG24 8EP, UK. **Date of revision:** November 2005.

Further information is available from: Shire Pharmaceuticals Limited, Hampshire International Business Park, Chineham, Basingstoke, Hampshire, RG24 8EP, UK. Tel: 01256 894000. Reminyl is a registered trademark of Shire Pharmaceutical Development Limited in the UK.

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