A guide to prescribing anti-dementia medication

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This article outlines a good practice guide to prescribing anti-dementia medication developed jointly by a lead nurse for memory services and a clinical pharmacist. The guide brings together current evidence to produce a concise prescribing guideline for practitioners.

As a lead nurse for memory services and a clinical pharmacist, we developed a good practice guide to prescribing anti-dementia medication (Kennedy and Sud, 2013). The guide brings together current research evidence to support prescribers in the safe use of medications covered by National Institute for Health and Care Excellence guidance for the treatment of Alzheimer’s disease (NICE, 2011). It is not intended to replace more comprehensive reference texts, but to offer a guide to good practice that is easily and readily accessible to practitioners. We hope taking a multidisciplinary approach will improve adoption and ownership.

Nurse-led care in memory clinics

Memory services are the recommended single point of access for all suspected cases of dementia (NICE, 2006), a growing area of service delivery. A large number of memory clinics are registered on a national database and encouraged to pursue accreditation with the Memory Services National Accreditation Programme. The coincident growth in non-medical prescribing over recent years means many clinics include a significant element of nurse-led review and prescribing, for which evidence suggests there is confidence in safety and quality (Page et al, 2008; Jones et al, 2007).

Although the good practice guide is not intended exclusively for non-medical prescribers, it is within this context that it was developed, to offer support and guidance to those involved in the treatment phase of memory services.

Anti-dementia drugs

The projected prevalence of dementia over the coming decade poses significant challenges to services in being able to meet targets for early diagnosis, access to treatment and post-diagnostic support.

The three acetylcholinesterase inhibitors (AChEIs) – donepezil, galantamine and rivastigmine – have been available since 1997. These provide symptomatic relief and, at best, may improve the quality of life for people by slowing the progression of cognitive decline.

Memantine, an NMDA receptor antagonist is now included within NICE guidance as an option for managing moderate Alzheimer’s disease in people who are intolerant of or have a contraindication to AChEIs, or those who have advanced stage Alzheimer’s disease.

However, evidence suggests that only 30% of people with Alzheimer’s who are entitled to receive anti-dementia medications are actually receiving them (Ballard, 2013). Despite efforts to tackle this (Banerjee, 2009), it remains the case that those with dementia are still at risk of inappropriate prescribing, particularly in relation to behavioural and psychological

5 key points

1 People over 65 face a one in 14 likelihood of developing dementia, and those over 80 a one in six likelihood
2 Only 30% of people with Alzheimer’s disease who are entitled to anti-dementia drugs actually receive them
3 Acetylcholinesterase inhibitors (AChEIs) provide symptomatic relief and may slow the progression of cognitive decline
4 Memantine is an option for managing moderate Alzheimer’s in those who should not take AChEIs
5 All anti-dementia drugs need retitration if more than seven days of doses have been missed
symptoms of dementia (BPSD), and the management of comorbidities.

The cholinergic hypothesis asserts that Alzheimer’s disease is caused by reduced synthesis of the neurotransmitter acetylcholine. This is one of a number of competing hypotheses. It forms the basis for three of the medications in use. Acetylcholinesterase inhibitors aim to reduce the rate at which acetylcholine is broken down, increasing its concentration. There is evidence of the efficacy of AChEIs in mild to moderate stages of Alzheimer’s (Ballard, 2013), and more recent evidence from the Domino AD trial shows their clinical benefit in the advanced stage (Howard et al, 2012).

Memantine is the first of a new class of drugs acting on the glutamatergic system by blocking NMDA-type glutamate receptors. The hypothesis that underpins memantine use suggests that glutamate is released in excessive amounts when brain cells are damaged as part of the disease process, which then in itself causes brain cells to be damaged further. Memantine is believed to offer some protection against the potential effects of excess glutamate.

There is no current drug treatment that will alter the underlying neuropathological disease process; current pharmacological treatment strategies offer some brief symptomatic relief. As with all psychotropic agents, therefore, expectations of treatment outcomes need to be carefully managed by the prescriber.

Adverse events and adherence

A study at one mental health assessment unit revealed errors in 56% of patients’ medications over four months (Brownlie et al, 2014). Given that this unit had systems in place to identify and correct such errors, the potential for harm via inappropriate prescribing is apparent, particularly in organisations where such stringent systems are not in place.

The risk of side-effects in AChEIs is well documented, the most common being nausea and vomiting due to cholinergic excess. Figures suggest this may occur in 10-20% of patients taking them. Less common effects include muscle cramp, bradycardia, decreased appetite and weight, and increased gastric acid production. Side-effects associated with memantine include dizziness, confusion and fatigue.

The safety profile of these medications has been questioned and examined, particularly in relation to AChEIs and cardiovascular risk. Some researchers have claimed they increase cardiovascular risk (McCain et al, 2007; Haibara et al, 1995), but methodological inconsistencies limit the generalisability of these claims. Nonetheless, careful monitoring of cardiovascular risks is clearly advised, and Rowland (2007) gives a pragmatic overview of this issue.

Dementia is not an illness exclusively of old age, with approximately 17,000 people in the UK under the age of 65 being affected. Statistically, however, those over 65 face a 1:14 likelihood, and those over 80 a 1:6 likelihood (Alzheimer’s Society, 2012).

Adherence to prescribed medications has been widely examined; reasons for poor adherence are multifactorial (dexterity, cognitive decline, use of over-the-counter medications and overly complex or poorly explained medication regimens are but a few).

Older people are more likely not only to experience adverse effects of medications, both individually and as a result of polypharmacy, but also to have more than one disease (Banning, 2009), which increases their vulnerability to side-effects. Physical changes in later life alter the way drugs are metabolised, and an understanding of the effects of altered renal and hepatic function is essential to safe prescribing.

Sections in the guideline

The good practice guideline includes a flowchart indicating content and providing a quick reference tool. It has been approved by the Leicestershire Partnership Trust prescribing group and the Leicestershire Medicines Strategy Group.

The guideline is broken down into seven sections:

- Choice of drug (including drugs for BPSD);
- Baseline monitoring;
- Comorbidity;
- Switching drugs (because of side-effects or lack of efficacy);
- Loss of efficacy;
- Missed doses;
- Discontinuation.

Two areas that are of primary significance – managing prescribing alongside comorbidities, and the management of missed doses are discussed below.

Managing comorbid conditions

Cardiovascular disease

Given the obvious complexities of prescribing anti-dementia drugs in older people, it is important for prescribers to be able to follow clear evidence-based pathways to maintain patient safety and reduce the risk of adverse effects.

Cardiovascular disease is a particular area of risk. Although the use of baseline ECG before treatment is started may vary between services, locally this is encouraged before referral and/or treatment. Although not a requirement stipulated in the summary of product characteristics (SPC) for any of these medications, pulse monitoring (given the potential risk of bradycardia) and blood pressure monitoring where clinically indicated (if there is evidence of postural hypotension or reports of dizziness or falls) are advisable at review.

In relation to cardiovascular disease, all drugs should be used with some caution, particularly where there is pre-existing disease such as sick sinus syndrome. Serious cardiac conditions may mean the use of memantine is favoured (Box 1).

Renal impairment

The kidneys are a consideration in the pharmacokinetics of any drug excreted predominantly through this route and the well-worn phrase in prescribing “start low, go slow” is apt, particularly as individual pharmacokinetics may vary.

Donepezil, for example, generally requires no dosage adjustment as clearance is not affected, although, as with any agent, careful monitoring for adverse events is still advisable. Memantine, conversely, requires more careful management in patients whose estimated glomerular filtration rate (eGFR) is below 49. Where there is evidence of moderate renal impairment (creatinine clearance/eGFR 30-49), the daily dose should be 10mg, but may be increased up to 20mg via standard dose regimens if tolerated. If, however, creatinine clearance/eGFR is between 5 and 29 (severe renal impairment), the daily dose should not exceed 10mg.

**BOX 1. AChEI CONTRAINDICATIONS**

Contraindications to AChEI therapy that may mean memantine is favoured for moderate Alzheimer’s disease include:
- Severe cardiovascular decompensation/heart failure or severe/unstable angina
- Serious supraventricular cardiac conduction problems and associated bradycardias (for example, second-degree heart block)
- Severe obstructive pulmonary disease
- Active peptic ulcer disease and other severe dyspeptic symptoms
- Significant bladder outflow obstruction
- Proven major intolerance of at least two AChEI drugs
Our intention was to bring together organisation and for our service users. safe prescribing are in place in our we have developed is intended as a first able to all who may benefit. The guide this diagnosis is safe, effective and avail - that the treatment that accompanies older people with suspected dementia. accessing mental health services for many take will continue to be the front door to Memory services in whatever form they been missed (Table 1).

<table>
<thead>
<tr>
<th>Drug</th>
<th>No of days missed</th>
<th>1-2 days</th>
<th>3-4 days</th>
<th>5-6 days</th>
<th>≥7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galantamine</td>
<td>No need to retitrate</td>
<td>No need to retitrate</td>
<td>No need to retitrate</td>
<td>Reccommence 8mg daily for 2-4 weeks, then 16mg daily for 2-4 weeks, then 24mg</td>
<td></td>
</tr>
<tr>
<td>Donepezil</td>
<td>No need to retitrate</td>
<td>No need to retitrate</td>
<td>No need to retitrate</td>
<td>5mg daily for two weeks, then 10mg daily</td>
<td></td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>No need to retitrate</td>
<td>1.5mg twice a day for one week, increasing dose at weekly intervals</td>
<td>1.5mg twice a day for 1 week, increasing dose at weekly intervals</td>
<td>1.5mg twice a day for one week, increasing dose at weekly intervals</td>
<td></td>
</tr>
<tr>
<td>Rivastigmine transdermal patch</td>
<td>No need to retitrate</td>
<td>4.6mg/24hrs for four weeks, 9.5mg/24hrs thereafter</td>
<td>4.6mg/24hrs for four weeks, 9.5mg/24hrs thereafter</td>
<td>4.6mg/24hrs for four weeks, 9.5mg/24hrs thereafter</td>
<td></td>
</tr>
<tr>
<td>Memantine</td>
<td>No need to retitrate</td>
<td>● If maintenance was 20mg daily retitrate up from 10mg, increasing dose at weekly intervals (or from 5mg if previous tolerability issues) ● If maintenance was 10mg daily retitrate up from 5mg, increasing dose at weekly intervals</td>
<td>● If maintenance dose was 20mg daily retitrate up from 10mg, increasing dose at weekly intervals (or from 5mg if previous tolerability issues) ● If maintenance dose was 10mg daily retitrate from 5mg, increasing dose at weekly intervals</td>
<td>Retitrate up to previous optimum dose as per standard dose escalation</td>
<td></td>
</tr>
</tbody>
</table>

Managing missed doses
As mentioned above, adherence is a variable, and patients may miss doses for reasons often beyond their control, such as delayed delivery or missed appointments.

Guidance to support prescribers in this area should provide safe recommendations that err on the side of caution and take account of any previous issues with tolerance. The recommendations we arrived at follow a pragmatic review of the SPC combined with anecdotal evidence and our practice experience.

Although missing one to two days would not warrant any alteration in dose upon restarting, the advice beyond three days starts to vary depending on the chosen drug, with all needing some sort of retitration if more than seven days has been missed (Table 1).

Safe, effective, available treatment
Memory services in whatever form they take will continue to be the front door to accessing mental health services for many older people with suspected dementia.

We have a responsibility to ensure that the treatment that accompanies this diagnosis is safe, effective and available to all who may benefit. The guide we have developed is intended as a first step towards ensuring that standards for safe prescribing are in place in our organisation and for our service users. Our intention was to bring together information in a clear, concise guide for practitioners.

As more people are given a diagnosis of Alzheimer’s disease, existing treatments will continue to be the mainstay of pharmacological intervention for a number of years. Antipsychotics continue to be over-used in the treatment of BPSD (Ballard 2013), and the use of memantine needs to become more commonplace, where appropriate, for these devastating symptoms.

The use of combination therapy is not examined in the guide; current evidence that it confers additional benefits is inconclusive and deserving of further study. The addition of memantine to an AChEI if BPSD develops is clearly good practice.

Evidence from the Domino AD trial supports not withdrawing anti-dementia treatments prematurely, with benefits continuing beyond what was originally believed (Howard et al, 2012).

If we are to improve treatment rates, it is important to ensure a consistent, safe process once treatment has started. By producing a good practice guide to prescribing anti-dementia medication, our intention is to support that aim, and welcome any comment. NT

● The guide can be found at: tinyurl.com/guide-anti-dementiamedication

References