Medication use in patients with dementia at the end of life
### Facts on dementia – ROI

- There are currently around 41,740 people with dementia, with the numbers expected to grow to between 141,000 and 147,000 by 2041.
- There are nearly 50,000 people in ROI who are involved in caring for someone with dementia. Family carers provide 57% of the value of informal care.
- The baseline cost of dementia in ROI is estimated at €400m.

### Facts on dementia – NI

- There are around 19,000 people with dementia in NI. It is expected there will be 23,000 people with dementia by 2017 and 60,000 by 2051.
- It is estimated around 1,400 deaths a year are directly attributable to dementia. Deaths could be reduced by half if the onset of dementia could be delayed by five years.
- Two thirds of people with dementia live in the community while one third live in a care home.

### Dementia policy – ROI

- The ROI government intended to launch a new national dementia strategy in 2010 but this has not yet been published.
- A Vision for Change (2006) is the strategic policy document for mental health in general. It makes 14 recommendations on the subject of mental health and older people.
- 6% of total public health expenditure is spent on mental health in the ROI.

### Dementia policy - NI

- A dementia strategy for NI, Improving Dementia Services in Northern Ireland, was published in November 2011.
- It proposed 44 actions to provide early diagnosis and support; improve access to supported living and assistive technologies; improve care; and enhance staff knowledge and skills.
- 8.4% of total public health expenditure is spent on mental health in NI.
Introduction

The global prevalence of dementia is likely to increase to approximately 115 million by 2050 (Alzheimer’s Disease International, 2009) and with a global cost estimated at $604 billion, it is clear that dementia is a major global public health issue. In Northern Ireland (NI), there are currently around 19,000 people with dementia (DHSS&PS, 2011), while a 2012 estimate suggests that there are 41,740 people with dementia in the Republic of Ireland (ROI) (Cahill et al., 2012).

Palliative care and medication use are important issues in dealing with end-of-life-stage dementia. As research into palliative care for patients with advanced dementia has been limited to date, CARDI funded a project, led by Dr. Carole Parsons of Queen’s University Belfast, as part of its grants programme. This project aimed to evaluate the extent to which patient-related factors influenced clinical decision-making with regard to medication use in patients with end-stage dementia. This research brief presents a summary of the findings from the full report, Assessment of factors which influence physician decision-making regarding medication use in patients with dementia at the end of life (Parsons, et al., 2012).

Key findings

• There is considerable variability in decision-making among NI and ROI doctors about continuation or discontinuation of some medications at the end of life in patients with dementia, especially in relation to antibiotics, and dementia medications including acetylcholinesterase inhibitors and memantine hydrochloride.

• This research showed that the presence of an advance directive did not necessarily have an effect on doctor decision-making regarding medications. Proper understanding of the legal basis of advance directives is crucial for doctors.

• Practice guidelines for the prescription of medications such as statins and anti-psychotics for dementia patients are necessary, and building the evidence base on medication use will help doctors to make decisions. There are currently NHS guidelines covering NI but no equivalent in ROI.

• The wishes and comfort of the patient and patient’s family should be at the forefront of decision making when it comes to end of life care in dementia.
Background

Previous studies of medication use in populations with a reduced life expectancy (not specific to dementia) have highlighted the prevalence of suboptimal and inappropriate medication use. However, research into palliative care for patients with advanced dementia has been limited, and there are very few studies which have examined the appropriateness of drug therapy among such patients. Giron et al. (2001) found that patients with dementia had a higher risk of drug duplication and were at an increased risk of being prescribed medicines with potent “anti-cholinergic” activity. The use of anti-cholinergic medications in dementia patients can be problematic as they may counteract the benefits of anti-dementia medications.

Older people with advanced dementia often have a wide variety of physical and psychological needs, leading to the prescribing of multiple medicines. Medications are often added to control symptoms associated with end of life. The use of multiple medications, or polypharmacy, in patients with advanced dementia nearing the end of their lives is of particular concern. It may be difficult to spot adverse effects if the patient cannot communicate verbally. It has been widely recognised that polypharmacy is linked to drug-drug interactions, adverse drug reactions and drug-disease interactions.

The decision to continue or discontinue medication or to withhold treatment for a patient with advanced dementia nearing the end of life is often a difficult one for a doctor, and the family, to make. The doctor often has to consider a number of ethical issues, as in many cases the patient is unable to make decisions for themselves. It can be difficult to estimate the life expectancy of a patient with severe dementia as the progression of the disease is unpredictable and another condition or illness may trigger death. The opinions of the patient’s family may also influence a doctor’s decision process regarding treatment.

Study design and scenarios

Parsons et al. (2012) used a factorial survey design for a questionnaire distributed to GPs and hospital doctors in both NI and ROI. It included a set of four scenarios designed to evaluate issues related to initiating, withholding, continuing or discontinuing specific medications in patients with end-stage dementia nearing death. A summary of the four scenarios and medical issues which the participant needed to decide on is included in Table 1. In each of the scenarios, the patient had end-stage dementia and the clinical status, including all other medications prescribed, was described.
For each scenario, the participant was asked if they would continue or discontinue the medications presented, whether or not they would make any additions or changes to the treatment regimen, and if so, what changes and why. Within each scenario, three separate patient-related characteristics were included as experimental conditions:

1. **Place of residence**: The patient was described as residing in either his/her own home, in a nursing home or as a hospital in-patient. Hospital practitioners were only allocated scenarios relating to patients in hospital, while GPs were allocated scenarios relating to both home residents and nursing home residents.

2. **Advance directive**: Patients were either described as having a signed advance directive expressing preference for supportive care as opposed to more aggressive treatment at end of life, or having no advance directive concerning treatment.

3. **Family involvement**: There were three levels of family involvement whereby the family desired active treatment measures to save the patient’s life, supportive treatment for symptoms only, and no family involvement.

When asked, the majority of GPs and hospital doctors considered the patients presented in the clinical scenarios to be typical of patients seen in their own practice, and indicated that their suggested management of these hypothetical patients was the same as they would provide for their own patients.
Research findings

The responses of doctors to each of the scenarios were statistically analysed in order to examine the impact of patient-related characteristics on decision making, as well as to compare decisions in NI with those taken in ROI. This section presents the findings for each of the key medications of interest. Figures 1-4 below show the variability of decision-making on whether or not to discontinue medications between GPs and hospital doctors in NI and ROI. This is followed by a discussion of each individual medication in the study.

[Graphs showing decision-making percentages for various medications in NI vs. ROI GPs and hospital physicians]

Source: Parsons et al. (2012)
Donepezil hydrochloride (acetylcholinesterase inhibitor)\(^1\)
In scenario B, doctors were more likely to discontinue use of donepezil hydrochloride when the family desired supportive treatment measures (compared to no family involvement), and when the doctor was resident in ROI compared to NI. The lack of evidence available to guide clinicians on when to discontinue therapy with acetylcholinesterase inhibitors and the reports of adverse events associated with discontinuation may explain the variation observed in the decisions.

There is current controversy regarding the use of acetylcholinesterase inhibitors (such as donepezil hydrochloride) in patients with severe dementia. This is due in part to the lack of randomised controlled trial data in institutionalised patients with more severe illness (Herrmann et al., 2007a). Also, the impact of discontinuing dementia medications in patients with end-stage dementia has not been well studied. While benefits at the end-stage of dementia are likely to be minimal, it is not yet known whether abrupt discontinuation is associated with a decline in cognitive, functional or behavioural status, or the time period over which such a decline occurs (Weschules et al., 2008). However, more recent research has suggested that continuation of donepezil in those with moderate to severe Alzheimer’s disease was associated with cognitive and functional benefits (Howard et al., 2012), thus generating continued debate in this area.

Memantine
Several studies suggest modest cognitive, functional and behavioural benefits of memantine hydrochloride in patients with moderate to severe dementia, but there is no convincing evidence on its efficacy at the end of life stage (Herrmann et al., 2008). The majority of respondents in a survey of hospice medical directors in the US did not consider acetylcholinesterase inhibitors or memantine to be effective in persons with end-stage dementia and recommended discontinuing these therapies to their families at the time of hospice admission. However, respondents also reported that almost three-quarters of families have difficulty stopping these therapies (Shega & Tozer, 2009) as this may result in increased cognitive decline.

Statins\(^2\)
There was less variability in decision making regarding the use of statins, yet many GPs did not discontinue their use, despite the fact that evidence shows they are no longer relevant at the end of life stage. It has been recognised that the benefits of statins versus the risks of myopathy (a muscular disease) and other adverse events are uncertain towards the end of life, as the benefits of these drugs are realised only after a period of months or years for most indications (Maddison et al., 2011). The potential risks of having elevated levels of lipids in the blood are also no longer relevant in patients with end-stage dementia (Tjia, et al., 2010). Therefore, apart from cases of a recent acute coronary syndrome or cerebrovascular problems, discontinuing statins toward the end of life is considered reasonable and continued administration to patients with end-stage dementia is regarded as highly questionable. The lack of a conclusive evidence base and guidelines for discontinuation of statins at the end of life may in part explain why some doctors did not recommend discontinuation of statins in this clinical scenario (Parsons et al., 2010).

Antipsychotic medications
Less variability in decision-making regarding antipsychotic use was found in the Parsons et al. (2012) research. Only a small proportion of both NI and ROI doctors

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\(^1\) These are commonly prescribed for cognition in the treatment of patients with dementia.

\(^2\) These work to reduce the plasma levels of lipids.
recommended discontinuation of the antipsychotic quetiapine. Concerns have been recently expressed about the use of this medication which is not licensed for use in dementia and recent NI guidelines indicate that “routine use of antipsychotics is not recommended in dementia and such use is unlicensed” (Health and Social Care Board 2011). While numerous studies have reported widespread prescribing of antipsychotics for older nursing home residents with dementia, it has been argued that there is no obvious need for long-term use and that attempts to taper and discontinue antipsychotic agents in patients with dementia should be undertaken at regular intervals. Concerns regarding poor-quality prescribing were highlighted by a UK Department of Health report (Department of Health, 2009).

There are several reasons why doctors may not want to discontinue antipsychotics. In Scenario D, it was indicated that the hypothetical patient was usually combative with caregivers, while many doctors may be uncertain as to the non-pharmacological alternatives to antipsychotic drugs doctors, particularly GPs, may also be reluctant to discontinue a medication which has been prescribed by another doctor.

**Prescription of antibiotics**

In addition to the decision whether or not to discontinue medication, respondents were asked whether or not they would actively prescribe an antibiotic in Scenario A. 53% of GPs in NI would prescribe, compared to 42% of hospital physicians. In ROI, 57% of GPs would prescribe, compared to 40% of hospital physicians. The results suggest that, in common with studies from the US, there is inconsistency among physicians in NI and ROI with regard to prescribing antibiotics for patients with advanced dementia. There are certain situations when a doctor was more likely to prescribe an antibiotic, such as when the patient did not have an advance directive, when the patient’s family wanted active treatment measures and when the patient was resident at home or in a nursing home (compared to a hospital).

Fever and recurring infections are common during the final stages of dementia, but the benefits of treating the infection using antibiotics, compared to managing symptoms, are unclear. Previous studies have shown a high prevalence of antibiotic use in patients with dementia who are approaching the end of life, yet they may not improve patient comfort (Givens et al., 2010). If a treatment prolongs survival but does not contribute to the comfort of a patient, the decision to prescribe or not to prescribe should be made with the wishes and best interests of the patient and family at heart.

**Policy implications**

The future of end of life care in patients with advanced dementia lies in a combined approach which incorporates clinical research, educational policies and initiatives aimed at increasing recognition of dementia as a terminal condition. It is crucial that all decisions made by the doctor take into consideration the best interests of the patient and patient’s families.

The findings from this study suggest that there can be considerable variability in decision-making among NI and ROI doctors about continuation or discontinuation of
some medications at the end of life in patients with dementia, especially in relation to antibiotics, acetylcholinesterase inhibitors and memantine hydrochloride. This variability was evident amongst both GPs and hospital doctors.

The study sought to examine the effect of patient-related factors and doctor’s country of practice on this variability. However, the amount of variance explained by the statistical analysis used was small, ranging from 2.3% of the variance in decisions to continue memantine hydrochloride (scenario B), to 7.3% of the variance in decisions to prescribe an antibiotic (scenario A). This underlines the fact that clinical decision-making is driven by very complex sets of factors. Some key factors are outlined below:

**Patient place of residence**

Across the five medications of interest, the effects of patient place of residence, and doctor’s country of practice appeared to have the strongest and most consistent effects on decision-making. The effect of these variables on decision-making can be summarised as:

- When the patient was resident in hospital it was less likely that an antibiotic would be prescribed, and more likely that statins and antipsychotics would be discontinued.
- If the doctor practised in ROI (compared to NI), it was less likely that antipsychotics would be discontinued.
- If the doctor practised in hospital in ROI (compared to hospital in NI), it was more likely that donepezil hydrochloride and memantine hydrochloride would be discontinued.

In addition, an antibiotic was more likely to be prescribed when the patient did not have an advance directive or the family desired active treatment measures.

**Practice guidelines**

The NI dementia strategy published in 2011 voices concerns about the use of antipsychotics. It shows research from England which indicates that only 20% of people with dementia being treated with antipsychotic medication will derive some benefit from the treatment (DHSS&PS, 2011).

This research underscored the importance of ensuring that doctors are aware of practice guidelines in the area. The UK National Institute for Health and Clinical Excellence (NICE), part of the NHS system, publishes clinical guidelines for high standards of healthcare and encouraging healthy living. The guidance on treatment of dementia patients (National Institute for Health and Clinical Excellence, 2006) states that patients with mild to moderate symptoms should not be prescribed antipsychotics due to increased risk of cerebrovascular adverse events and death. Those with severe non-cognitive symptoms can be prescribed antipsychotics, but only under strict conditions, including a discussion with patient and family regarding the benefits. Prescription of statins is not recommended for primary prevention of dementia.

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3 These effects may be due to the location of the patient or to the speciality of the doctor, as decisions about patients in hospital were provided by hospital doctors only and decisions about patients in nursing homes or own homes were provided by GPs only.
The NICE guidelines on dementia also lay out conditions for the prescription of AChE inhibitors and memantine. These include the regular review of treatment, and that the medications should only be continued when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms (National Institute for Health and Clinical Excellence, 2006).

The Health Information and Quality Authority in ROI has guidelines that recommend a review of medications for patients of nursing homes every three months (HIQA, 2009). The Medical Council in ROI also publishes the *Guide to Professional Conduct and Ethics for Registered Medical Practitioners*, which has a section on end of life care. It notes that:

“There is no obligation on you to start or continue a treatment, or artificial nutrition and hydration, that is futile or disproportionately burdensome, even if such treatment may prolong life. You should carefully consider when to start and when to stop attempts to prolong life, while ensuring that patients receive appropriate pain management and relief from distress”.

The guide also makes it clear that the right of patients to refuse medical treatment or to request the withdrawal or treatment should be respected, as should an advance directive (Medical Council, 2012).

However, there are no specific guidelines for prescribing medications such as antipsychotics, statins or AChE inhibitors in ROI. Such guidance may help to solve the issue of variation in doctor decision making, along with building the evidence base on benefits and disadvantages of medications.

**Advance Directives**

Parsons et al. (2012) shows that the presence of an advance directive did not necessarily have an effect on doctor decision-making regarding the medications of interest examined in the scenarios, with the exception of initiation of an antibiotic. This may be related to doctors’ lack of awareness or understanding regarding advance directives in patients with advanced dementia, or may be due to the as yet untested legal status of such directives in NI and ROI. Education strategies to raise doctors’ awareness and understanding of advance directives should therefore be implemented.

**Legal status of advance directives**

An advance directive may be defined as a written document giving direction and guidance for healthcare decisions at a time of future incompetence (Medical Council, 2012). There may be circumstances, such as a diagnosis of dementia, in which a competent adult wants to give instructions about how he or she should be treated if they become incompetent in the future. An advance directive of this kind is usually confined to a refusal of future medical treatment. An advance instruction to *provide* particular treatment would not be binding on medical staff, as patients do not generally have the right to insist on particular treatment.
As long as the patient is competent at the time, has not changed their mind and the directive covers the situation at hand, it is binding on medical staff. To date in ROI, there have been no cases directly on the issue of advance directives, nor are there any statutory provisions. However, in *Re a Ward of Court* [1996] 2 IR 79, the decision was made by the Supreme Court that the right to life as guaranteed by the constitution implied a right to die a natural death.

An advance decision to refuse treatment made by an adult is legally binding in England and Wales, under the terms of the Mental Capacity Act 2005. In Scotland and NI, advance directives are governed by common law, but the principles applied are very similar in all jurisdictions of the UK. The directive must specify the treatments being refused, and in what circumstances, and may be made verbally or in writing. If, however, the refusal relates to life-sustaining treatment, the decision must be in writing, signed and witnessed. It must also clearly state that the refusal stands even if it will place the individual’s life at risk (Medical Protection Society, 2012).

**Conclusion**

Making decisions on medication at the end of a patient’s life is a complicated and difficult part of a doctor’s work. It is clear that there are many factors which influence this decision making. What emerges from the Parsons et al. (2012) research is that where there is variability in decision making on particular medications or in particular situations, further research is required. This will contribute to more standardised clinical decision making. Providing practice guidelines, such as the NICE guidelines, for the prescription of all medications in patients with advanced dementia who are approaching the end of life would ensure that decision making is being made on the best available evidence.

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