Using antipsychotics in dementia patients creates a clinical and ethical dilemma

Dementia is accompanied by varying degrees of behavioural and psychological symptoms in 50–80% of patients, which can cause significant distress both for the patient and for their families. Management of these symptoms, however, is fraught with clinical and ethical considerations explains Delia Bishara.

Introduction

Dementia is a progressive neurodegenerative disease characterised by deterioration in cognitive and functional abilities. The accompanying behavioural and psychological symptoms of dementia (BPSD) include psychosis, agitation and mood disorder[1] affecting 50% to 80% of patients to varying degrees.[2] These neuropsychiatric symptoms frequently hold many adverse clinical repercussions and generally worsen prognosis. They have been shown to accelerate cognitive decline,[3,4] decrease quality of life[5] and may also be associated with higher mortality,[6,7] although the results of various studies have disputed this.[3,4] In addition the distress experienced by patients and their families results in considerable carer burden[8] thus increasing risk of institutionalization, nursing home placement[9] and elevating cost of care.[10]

Management of BPSD in nursing homes

The safe and effective management of these symptoms has become a global challenge over the last few years. Various classes of psychotropic agents have traditionally been used off-label including anxiolytics, anticonvulsants, antidepressants, cognitive enhancers and antipsychotics. For more than half a century there has been an appreciable concern about the abundant and sometimes unnecessary use of antipsychotics in residential and nursing homes.[11] Antipsychotic prescribing rates in UK care homes have been reported to be in the range of 24–28%[12] with one study finding that 88% of these prescriptions were deemed inappropriate.[13]

Efficacy and safety of antipsychotics in BPSD

Risperidone is the only drug currently licensed in the UK for BPSD. It obtained its licence very recently and is indicated 'for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others'.[14]

The practice of using antipsychotics in BPSD has been supported by numerous randomised controlled trials and meta-analyses. They are the most widely studied pharmacological intervention for the non-cognitive symptoms associated with dementia and have demonstrated modest but consistent efficacy.[15] In view of the associated movement disorders limiting the use of typical antipsychotics, atypical antipsychotics progressively became the preferred option after their introduction in the 1990s. Furthermore, some studies suggested that atypicals actually possessed neuroprotective properties in addition to their antipsychotic action.[16,17] Risperidone and olanzapine were noted to have the best evidence for efficacy in BPSD[18] leading to their widespread use in this patient group.

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The use of atypicals came under scrutiny in 2004 following suggestions that they may be linked to an increased risk of cerebrovascular adverse events (CVAEs) compared with placebo. Analysis of both published and unpublished data revealed a three-fold increase in the risk of stroke for risperidone when used in older patients with dementia and a similar risk for olanzapine. Based on these findings, the Committee on the Safety of Medicines (CSM) issued a warning against the use of risperidone and olanzapine for behavioural symptoms of dementia.[19] These warnings have been extended to include all atypical antipsychotics as well as conventional antipsychotics[20] in view of more recent data. The inclusion of a warning about a possible risk of cerebrovascular events has now been added to SPCs for all typical and atypical antipsychotics.

The interpretation of these CVAE risks is far from straight forward. Firstly, the studies involved were specifically designed and powered to determine efficacy and not a relationship between antipsychotics and CVAEs. In addition, the diagnosis

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of CVAEs was broad, not operationally defined and based on spontaneous reports, which were not validated.[21]

A review of the available evidence by the European Medicines Agency (EMEA) has concluded that typical antipsychotics are also associated with an increased risk of death comparable to that seen with atypicals — and potentially even greater.[20,22,23] Although the results of some studies suggest an even greater risk of mortality is observed with conventional antipsychotics compared with atypical antipsychotics, the report concluded that this could not be confirmed because of the methodological limitations of the studies. In addition, there was insufficient evidence to determine whether the risk of death differs from one medicine to another, so the risk is assumed to apply to all medicines in the class.[20]

Of note are the results from a recent long-term study (lasting 24–54 months), which found that the risk of mortality progressively increased over time for antipsychotic-treated patients (continued for 12 months) compared with those who were switched to placebo.[24] During the first 12 months, the cumulative probability of survival was 70% (antipsychotics) vs 77% (placebo); at 24 months survival was 46% vs 71% and at 36 months it was 30% vs 59% (antipsychotics vs placebo respectively). This study clearly suggests that antipsychotics should be avoided whenever possible.

Several mechanisms have been postulated for the underlying causes of CVAEs with antipsychotics.[25] Orthostatic hypotension, a common adverse effect of antipsychotics, may aggravate the deficit in cerebral perfusion in an individual with cerebrovascular insufficiency or atherosclerosis. Similarly, tachycardia may decrease cerebral perfusion or dislodge a thrombus in a patient with atrial fibrillation. After an episode of orthostatic hypotension, there could also be a rebound excess of catecholamines with vasoconstriction thus also aggravating cerebral insufficiency. In addition, hyperprolactinaemia could, in theory, accelerate atherosclerosis and sedation might cause dehydration and haemoconcentration. All of these drug-induced side-effects are possible mechanisms for increased risk of cerebrovascular events.[25]

Antipsychotics have also been associated with significantly greater cognitive decline compared with placebo[26,27] as well as increased risk of falls among the elderly population[28] — presumably because of their autonomic and sedative effects — leaving patients vulnerable to hip fractures.[29]

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In 2008 after increasing concerns over the safety of antipsychotics in dementia, MPs in Britain urged the Government to stop the 'dangerous over prescribing' of these agents to people in care homes with dementia.[30] As a result, the Government announced proposals to develop a national dementia strategy set to tackle these issues.[30] Consultation on this document has now been completed and the guidance document, *Living well with dementia: a national dementia strategy*, was published by the Department of Health as *Pharmacy in Practice* went to press.

Alternative pharmacological agents

Regrettably, there are few pharmacological alternatives to antipsychotic drug use in the management of dementia. Certain antidepressants,[31,32] mood stabilisers,[33,34] benzodiazepines[35] and cognitive enhancers[36–39] may afford some benefit in BPSD, but evidence for this has been inconclusive and these agents have also been associated with potentially serious adverse effects. In the extension phase of a randomised controlled trial with valproate, seven out of the 39 patients who enrolled in the study died during the 12-week period.[40] Benzodiazepines may hasten cognitive decline[37] and contribute to increased frequency of falls and hip fractures in the elderly.[41,42] In addition, concerns over the potential cardiac adverse effects associated with cholinesterase inhibitors arose from observations made in controlled trials of galantamine in mild cognitive impairment (MCI) in which increased mortality was associated with galantamine use compared with placebo. Although no specific cause of death was predominant half of the deaths reported were caused by cardiovascular disorders.[43]

In 2005, the National Institute for Health and Clinical Excellence (NICE) working in conjunction with the Social Care Institute of Excellence (SCIE) issued guidance restricting the use of cholinesterase inhibitors and memantine in Alzheimer's disease. This generated much controversy among scientists, clinicians, manufacturers and interested members of the public — including patients and carers — in view of this further restriction to the already limited treatment options for BPSD. The debate on the use of anti-Alzheimer's drugs continues, with pharmaceutical companies supported by the Alzheimer's Society mounting a legal battle against NICE's contentious decision.[44]

Alternative therapies

Non-pharmacological alternatives to managing BPSD exist but data supporting their evidence are scarce and availability of such therapies is limited within the NHS.[45] Psychological therapies centred on individual patients' behaviour have generally been successful for the management of neuropsychiatric symptoms and the positive effects can last for months. Music therapy

and Snoezelen (specially designed rooms with soothing and stimulating environment) have also proven to be somewhat useful but have no long-term effects. The cost and complexity of Snoezelen rooms are the main barriers for their use.[46] The lack of high-quality research into these therapies and limited resources have considerably restricted their use to date.

A number of different complementary therapies have been used in the management of BPSD including massage, reflexology, homeopathy and aromatherapy. Aromatherapy is one of the fastest growing of these therapies, and extracts from lavender and Melissa balm are most commonly used.[47] Some positive results from controlled trials have shown significant reduction in agitation[48] although the evidence base is still relatively sparse and the side-effect profile virtually unexplored.[49]

The dilemma

The complexity of managing the behavioural and psychological symptoms of dementia has generated a longstanding debate. Considering the distress to patients and their carers that these symptoms can cause, as well as the resulting clinical repercussions, the evidence base for pharmacological treatment is generally poor. The best evidence lies with risperidone and olanzapine but the CSM advice has now considerably reduced their use and left clinicians in a quandary. Prescribers

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are faced with having to resort to other agents for the management of BPSD. Many now prescribe alternative atypical antipsychotics such as quetiapine, which has less convincing evidence for efficacy, or a typical antipsychotic with similar or possibly even worse adverse effects. As in all areas of medicine, weighing the risks versus the clinical benefits is common practice but when the risks are high with minimal benefits and no viable alternatives a clinical and ethical dilemma emerges.

Best practice

In view of the poor evidence base and serious adverse effects linked to the current agents used in BPSD, it is extremely difficult to make specific recommendations concerning the safe and effective management of these symptoms. The following approach, however, may prove to be a useful guide.

Primarily, potential physical causes aggravating BPSD should be eliminated. These may include pain, constipation or infections — especially urinary tract and chest infections, which are most commonly seen in the elderly population. Once a physical cause has been excluded, specific symptoms should be targeted when selecting therapy. Evidently, non-pharmacological options must always be considered first. It is clear that the NHS needs to increase resources in this area and invest in more staff, adequate training and make non-pharmacological therapies more widely available to patients. All treatment decisions should be tailored to the individual needs of the patient.

Although there is some evidence of indiscriminate and careless prescribing of antipsychotics in the elderly population, it is not to say that they may not occasionally be required in some patients. While avoiding antipsychotics or other agents may be an option in certain cases patients and their families must also be made aware of and understand the risks of having no treatment at all. This might expose the individual, their fellow residents and carers to dangerous situations. The use of antipsychotics in elderly patients with dementia should, however, certainly be restricted to experts in the field. A possible, if somewhat Draconian solution, would be to preclude GPs from prescribing them and only allow old age psychiatrists to do so following a comprehensive review and sufficient justification from a risk-benefit analysis for each patient. Prescriptions may also be prospectively time-limited with the expectation of expiry thereby forcing clinicians to review treatment rather than antipsychotics being continued unnecessarily. In addition, the risks must be clearly discussed with both the patient, if they have capacity, and/or their families.

If antipsychotics are to be used, the lowest dose possible should be administered for the shortest period necessary. There should be ongoing review and consideration of treatment appropriateness as well as close monitoring for adverse effects.

If antipsychotics are to be used, the lowest dose possible should be administered for the shortest period necessary. There should be ongoing review and consideration of treatment appropriateness as well as close monitoring for adverse effects. Reasons for specific drug choices should be documented clearly in the medical notes including any discussions with the patient, their family or carers. In view of the difficult and confusing process for selecting a treatment option for BPSD, it is vital that clinicians stay well informed and up-to-date as new research emerges. ✣

Declarations of interest

The author has no interests to declare.

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Note: After a period of consultation the national dementia strategy was published as *Pharmacy in Practice* went to press. The guidance document, *Living well with dementia: a national dementia strategy*, was published by the Department of Health and is available for download at http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_094058

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