

Pharmacological management of behavioural disturbance in patients with dementia

Management of behavioural disturbance in the setting of dementia can be challenging. There are many potential causes including poor physical health, prescribed drugs, depression, impaired vision and hearing as well as numerous environmental factors. Drug prescribing in patients with behavioural disturbance has evolved over the years in a haphazard and anecdotal way. As a result patients have been exposed to a wide range of drugs, some of which have significant side-effects.

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The prevalence of dementia increases from approximately 0.7% in those aged 60–64 years, doubling every five years or so to nearly 40% in those aged 90–95 years. The symptoms and signs of dementia consist both of features attributable directly to cognitive deficits and also to non-cognitive features some of which include disturbed behaviours (eg, aggression, wandering, eating disorders) and psychiatric symptoms (eg, hallucinations, delusions and affective disturbances). These are sometimes referred to as Behavioural and Psychological Symptoms of Dementia (BPSD), a term introduced by the International Psychogeriatric Association in the early 1990s to facilitate clinical trials in this area but the term has never been popular in clinical practice. The non-cognitive symptoms often lead to behavioural disturbance and considerable distress for patients as well as significant carer stress¹ that often results in a residential placement.

In community settings, the highest prevalence rates for behavioural disturbance in patients with dementia are seen in patients in 24-hour care settings and in some specialist settings (eg, EMI Homes) where the prevalence can be as high as 90%. Few differences have been found between the prevalence rates in patients

with Alzheimer's disease and vascular dementia² but rates may be higher in patients with Lewy body dementia possibly because of the presence of the prominent visual hallucinations.

Aetiology

Many different factors may be associated with behavioural problems in patients with dementia. Physical illness such as poorly controlled pain, diabetes with impaired glucose metabolism, dehydration, hypoxia, electrolyte disturbances and heart failure are all common causes but this is not an exhaustive list. Drugs, especially those with anticholinergic side-effects such as tricyclic antidepressants (eg, imipramine) and the older antipsychotics (eg, chlorpromazine) may cause delirium and further impair memory in patients with dementia.³ Other factors that may lead to behavioural disturbance include depression, psychotic symptoms and communication difficulties especially due to dysphasia. Environmental factors such as noisy and over-stimulating environments, social isolation and visual and auditory sensory impairments may all contribute or be the cause of behavioural disturbance. In addition, age-related neurotransmitter changes

(acetylcholine, dopamine, noradrenaline and serotonin), damage to specific brain regions responsible for emotional activity (parahippocampal gyrus, dorsal raphe and locus coeruleus) and cortical hypometabolism have also been proposed as possible neurobiological causes.⁴

Assessment and management

Patients will require a full assessment including medical and psychiatric history, mental state and a thorough physical examination as well as any supplementary investigations. Any specific illness should be treated.

Before considering specific pharmacological treatments, especially antipsychotics, non-pharmacological approaches should always be tried. Several interventions for an individual patient are more likely to be effective than a single approach so a combination of good physical healthcare combined with psychological and pharmacological interventions might need to be considered in complex or difficult to treat patients.⁵ There are a wide range of non-pharmacological interventions that can be tried and three broad theoretical models are summarised in box 1.⁶

In the unmet needs model, the intervention aims to address the underlying needs that are causing the inappropriate behaviour. Sensory deprivation, boredom and loneliness are thought to be common causes for inappropriate behaviour in nursing homes. The behavioural/learning model assumes a connection between antecedents, behaviour and consequences. Treatments that focus on reduced stimulation levels or relaxation techniques (eg, massage) are based on the assumption that the dementia process results in greater environmental vulnerability and a lower threshold at which stimuli affect behaviour.

Pharmacological management

Drug prescribing in patients with behavioural disturbance has evolved over the years in a haphazard and anecdotal way. As a result patients have been exposed to a wide range of drugs, some of which have significant side-effects.⁷ In the UK, no drugs are currently licensed for the management of behavioural disturbance in the setting of dementia. In the US, the use of drugs to manage behavioural disturbance

Box 1: Models for non-pharmacological interventions

- The unmet needs model
- A behavioural/learning model
- An environmental vulnerability/reduced stress-threshold model.

in this context is not permitted unless there is clear evidence that psychological treatments have been tried and demonstrated to have been unsuccessful.⁸ However, a number of drug groups have been tried, especially antipsychotics, and these are now discussed in more detail.

Antipsychotics

It is now over half a century since chlorpromazine, the first modern synthetic antipsychotic was used in clinical practice. Since then a wide range of antipsychotics have been developed. The newer drugs are usually referred to as "atypicals" and these are said to have improved efficacy, side-effects and safety compared with older drugs such as haloperidol and chlorpromazine. However, most of this development and research has focused on schizophrenia rather than dementia. Guidance from NICE in 2002 on schizophrenia and atypical antipsychotics was well received but use of antipsychotics in older people was not considered.⁹ The National Service Framework for Older People did include a Medicines Code that included a short section on antipsychotic medication. Although this highlighted the misuse of antipsychotics in older people, prescribing guidance was not offered.¹⁰

Typical antipsychotics have limited use in older people compared with atypical antipsychotics because of their side-effects and particularly their propensity to cause delirium (eg, chlorpromazine) and extrapyramidal side-effects (EPSEs) especially with haloperidol. Until a few years ago thioridazine was extensively used in the UK but this use has now stopped because of the association with sudden death from cardiovascular events. There is some evidence that the older drugs, despite their problems, have some clinical benefit.¹¹

However, there is considerably more evidence for the atypical antipsychotics and especially risperidone and olanzapine but these studies are now fairly old.¹²⁻¹⁶ There is less evidence for other antipsychotics although two recent studies reported benefit with quetiapine.^{17,18}

Data from the relatively large number of good trials examining risperidone and olanzapine for the management of behavioural problems in dementia from about 2000 started to suggest that these two drugs might be associated with an increased risk of cerebrovascular events in older people with dementia.¹⁹ These concerns led to a statement being issued by the Committee on Safety of Medicines in the UK in March 2004²⁰ which noted that: "There is clear evidence of an increased risk of stroke in elderly patients with dementia who are treated with risperidone and olanzapine. The magnitude of the risk is sufficient to outweigh likely benefits in the treatment of behavioural disturbances associated with dementia and is a cause of concern in any patient with a high baseline risk of stroke."

The risk of stroke disease was 3.3% compared with 1.1% in the placebo group. The Committee on Safety of Medicines recommended that risperidone and olanzapine should not be used for the treatment of behavioural symptoms in dementia. In the same month the Working Group for the Faculty for the Psychiatry of Old Age, the Royal College of General Practitioners, the British Geriatrics Society and the Alzheimer's Society²¹ issued advice. A range of alternative medications were suggested including haloperidol, which paradoxically is also known to increase the risk of stroke disease in patients with dementia. In April 2005 the US Food and Drug Administration²² recommended not using atypical antipsychotics for the management of patients with dementia and behavioural disturbance because of increased mortality compared with placebo (4.5% versus 2.6%). The following year a meta-analysis of the efficacy and safety of atypicals for behavioural problems in the setting of dementia suggested an increased mortality of 1.7 compared with placebo.²³ In addition, the Faculty for the Psychiatry of Old Age further suggested that when drugs are used (including antipsychotics) these should be for specific target symptoms such as depression or psychosis, the starting dose should be low and treatments should be time limited. If an atypical is proposed, all the relevant factors should be considered and the decision clearly

documented with a clear review date.²⁴

Following the Committee on Safety of Medicines advice further evidence emerged for an association with cerebrovascular events. In 2005 Herrmann and Lanctot reassessed pooled results from 11 randomised controlled trials of risperidone and olanzapine in elderly dementia subjects and found an increased risk of cerebrovascular events but reanalysis of the risperidone trials suggested non-specific events that might not have been strokes but could have caused the increased incidence.²⁵ They also suggested that due to an increased number of mixed dementia patients in the risperidone trials, it could account for the higher rate of cerebrovascular events. Overall they felt further clarification was needed about the association between cerebrovascular events and antipsychotics.

In the following year a Cochrane review of 16 placebo-controlled studies of atypical antipsychotics for the treatment of aggression and psychosis in patients with Alzheimer's disease found significant improvement in patients treated with olanzapine and risperidone but also a significantly higher incidence of serious adverse cerebrovascular events, including stroke.²³ The authors recommended that risperidone and olanzapine should not be used routinely to treat dementia patients with aggression or psychosis. In addition, Percudani et al²⁶ in a large population based retrospective study found an increased risk of cerebrovascular events associated with risperidone but not with other atypicals.

However, in two large retrospective population based cohort studies of 32,000 and 11,000 patients an association between atypicals and increased risk of stroke was not found.^{27,28} A number of other studies have also failed to find an association.²⁹

Potential mechanisms for the association of atypical antipsychotics and cerebrovascular events have been postulated including thromboembolic events, cardiovascular effects (orthostatic hypotension, arrhythmias), excessive sedation causing dehydration and haemoconcentration and hypoprolactinaemia. However evidence to support these mechanisms is sparse.³⁰

Some authors have suggested that because of the cerebrovascular risks of using antipsychotics in patients with dementia, these drugs should be used significantly less.³¹ Others take the view that these drugs can be very effective and that a more appropriate strategy would be to more carefully manage risks.³²

There is undoubtedly evidence that drugs are effective in the setting of dementia. However, because of the weight of evidence suggesting an association with cerebrovascular events as well as the CSM advice, this suggests that these drugs should not be used first line and only after a range of other non-pharmacological and drug treatments have been tried.

Anti-dementia drugs

Given their mechanism of action, these drugs would seem to be a logical choice when considering pharmacological options for the management of behavioural disturbance in dementia. There have been a number of good general reviews of this area and although they are now a few years old these are still very relevant.^{33,34} More specifically there have been a number of studies of individual anti-dementia drugs showing benefit in the management of behavioural problems in dementia including donepezil, galantamine, rivastigmine and memantine.³⁵⁻⁴⁰

Other drugs

Depression is common in patients with dementia and as many as 40% of patients with dementia have significant depressive symptoms at some stage during their illness,⁴¹ although depression may be difficult to diagnose in patients with dementia. Data for the management of behavioural disturbance in dementia using antidepressants is relatively scarce. In Germany, Austria and Switzerland selective serotonin reuptake inhibitors (SSRIs) are used in approximately 30% of patients as first-line treatments.⁴² Trazodone and SSRIs have been the subject of several small studies with positive results^{43,44} but information is very limited. However, in clinical practice the authors have found that antidepressants can be very effective in carefully selected patients especially in those with marked irritability.

The efficacy and tolerability of anticonvulsants such as carbamazepine and sodium valproate still need to be firmly established although there have been some positive reports including case reports, chart reviews, and case series. In addition, the authors have found that sodium valproate can be particularly effective for those with motor disturbance and it appears to be very well

tolerated. However, a recent good review concluded that anticonvulsants cannot be recommended for routine use due to the limited evidence base.⁴⁵

Benzodiazepines also have a useful role but should be used mainly for short-term management because of the risks of side-effects, especially falls and of tolerance developing. The most commonly used drug is lorazepam and there is a reasonable evidence base for this. However, as a group these drugs can cause significant sedation, postural hypotension and memory impairment so they need to be used with care.

Buspirone was approved by the Food and Drug Administration (US) in 1986 for generalised anxiety disorder but has also been used for a number of other indications including behavioural symptoms in dementia.⁴⁶ However, there has been little published data in this area.

There have been studies on the use of beta-blockers and oestrogen therapy with regards to management of behavioural and psychological symptoms in dementia. However, the evidence of their usefulness in this area remains unclear and further research is needed.

Conclusion

Management of behavioural disturbance in the setting of dementia can be challenging. There are many potential causes including poor physical health, prescribed drugs, depression, impaired vision and hearing as well as numerous environmental factors. Treatment should include the management of any specific causes combined with psychological and where appropriate pharmacological interventions. However, there may be problems implementing non-pharmacological interventions due to widespread difficulties getting access to psychological interventions. In our opinion there needs to be a training programme and strategy similar to the government commitment to cognitive behavioural therapy for depression.

The evidence base for drug interventions is relatively poor considering the size of the clinical problem and the distress such disturbance causes. For many years the principal pharmacological treatment has been with the antipsychotics and to date the best evidence base is with risperidone and olanzapine. However, over the past 4 to 5 years concerns about the increased risk of stroke disease has led to a significant reduction in

their use in patients with dementia. Unfortunately very little research is now being done in this area resulting in drugs being prescribed despite the paucity of the evidence base. If antipsychotics are used they should be used as a last resort and only after careful consideration, discussion and documentation with regular reviews and discontinuation at the earliest opportunity.

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