Pharmacological alternatives to antipsychotics to manage BPSD

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Non-pharmacological management remains the initial approach for behavioural and psychological symptoms of dementia (BPSD). However, pharmacological management has a role in specific situations. Here, the authors examine the pharmacological management of elderly patients with dementia and challenging behaviour and aim to raise awareness of the risk of complications associated with first- and second-generation antipsychotic medications.

Dementia is a progressive and largely irreversible clinical syndrome characterised by widespread impairment of mental function.\(^1\) Behavioural and psychological symptoms of dementia (BPSD) is a term introduced in the 1990s,\(^2\) with an estimated incidence of up to 75% of people with dementia who may be affected by non-cognitive symptoms and challenging behaviour.\(^1\) Dementia patients can experience changes in personality, self-neglect, apathy, depression, aggression, restlessness, wandering, disruptive vocal activity, sleep disturbance, and disinhibited sexual behaviour. Table 1 summarises BPSD frequency depending on Alzheimer’s disease (AD) stages; the domains were evaluated using the Neuropsychiatric Inventory.

Apathy is a disorder of motivation that persists over time and it is the most common and persistent symptom of AD\(^3\). Its formal diagnosis requires the following criteria: diminished motivation for at least four weeks, and two of the three dimensions of apathy (reduced goal-directed behaviour; goal-directed cognitive activity, and emotions). These symptoms result in functional impairment not exclusively explained by physical disability or a substance induced effect.\(^4\)

It appears that depression, apathy, delusions, anxiety and agitation are more frequent in severe compared with mild dementia; while hallucinations are less frequent in severe compared with moderate dementia (Table 1).

Sexually disinhibited behaviours are quite common, with prevalence between 2–17%, with almost equal frequency in men and women.\(^5\) These may include explicit sexual comments, exposing the breasts or genitals in public, or touching someone inappropriately. While some behaviour is still ambiguous such as undressing outside the bathroom or bedroom. There is no widely agreed definition for an abnormal sexual behaviour in dementia; it is based on judging what is normal for a person in a particular situation. Accordingly, there is a difference based on the setting, for example if the patient is at home, a residential home or in hospital, depending on the level of risk or discomfort for others.\(^5\)

People suffering from BPSD should be offered an assessment at an early opportunity including physical health, depression, undetected pain, medication adverse effects and psychosocial factors.\(^1\) Individually tailored care plans should be developed, recorded in the notes and reviewed regularly.\(^1\)

Can certain drugs increase BPSD risk?
Medications with anticholinergic activities have a potential to cause symptoms of BPSD such as delirium and confusion. These medications include tricyclic antidepressants, first-generation antipsychotics, urinary

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Table 1. Frequency of behavioural and psychological symptoms of dementia across Alzheimer's disease stages

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mild3</th>
<th>Moderate 29</th>
<th>Severe3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apathy</td>
<td>47%</td>
<td>67%</td>
<td>92%</td>
</tr>
<tr>
<td>Agitation</td>
<td>47%</td>
<td>45%</td>
<td>85%</td>
</tr>
<tr>
<td>Aberrant motor behaviour</td>
<td>12%</td>
<td>53%</td>
<td>84%</td>
</tr>
<tr>
<td>Depression</td>
<td>12%</td>
<td>52%</td>
<td>62%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>24%</td>
<td>49%</td>
<td>54%</td>
</tr>
<tr>
<td>Irritability</td>
<td>35%</td>
<td>35%</td>
<td>54%</td>
</tr>
<tr>
<td>Delusions</td>
<td>12%</td>
<td>37%</td>
<td>31%</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>35%</td>
<td>22%</td>
<td>31%</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>12%</td>
<td>24%</td>
<td>8%</td>
</tr>
<tr>
<td>Euphoria</td>
<td>18%</td>
<td>8%</td>
<td>8%</td>
</tr>
</tbody>
</table>
retention medications like oxybutynin, H2-antagonists such as cimetidine, antibiotics such as quinolones, and anticonvulsants such as carbamazepine. Furthermore, some medications are known to be associated with side-effects, such as an increased risk of depression with beta-blockers and anticonvulsants. Drugs causing symptoms of psychosis include systemic steroids and NSAIDS.6

**Can pharmacological management be the first response to BPSD?**

Non-pharmacological management should be the first response. However, pharmacological treatment may be an appropriate first response if there is a specific indication. For example, psychosis or depression, severe symptoms, distressing to patients or others where treatment is urgently needed and the behaviour has no clear situational trigger or occurs in a setting where carers cannot cope.7 In addition, pharmacological treatment has a role if there is an immediate risk of harm to the patient or others.1 There is a need for carers in care homes to have further dementia training. For example, a recent survey in the west Midlands on perceptions about the levels of dementia training among staff in dementia-registered care homes identified that 19% of staff who participated in the survey felt that further training is needed in BPSD.8

Antipsychotics used to treat BPSD are arbitrarily categorised as typical (first generation) and atypical (second generation). Antipsychotics block dopamine (DA) receptors in the mesolimbic and mesocortical, and the therapeutic efficacy is thought to correlate with their affinity for D2-receptors, although other mechanisms are likely to contribute. The binding to basal ganglia and pituitary gland D2-receptors lead to their extensive side-effects.

Atypical antipsychotics such as olanzapine have a relatively low affinity for D2-receptors, which does not correlate with their clinically effective dose. They are 5-HT2 and D4-receptors antagonists with effectiveness in physical aggression, agitation and psychosis.9-11 There is a modest but significant effectiveness in treatment of aggression in AD.12

On the other hand, there have been concerns regarding the safety of administering atypical antipsychotics to elderly, as shown in the Committee on Safety of Medicines (CSM) alert on atypical antipsychotic use in BPSD patients.13 This followed manufacturer data, which showed an increased risk of cerebrovascular adverse events ranging from transient ischemic attacks to strokes associated with risperidone and olanzapine. The CSM suggested a three-fold increased risk of cardiovascular adverse effects from 1.1% to 3.3% over a 12-week period. In addition, risperidone is associated with additional risk of death when co-prescribed with furosemide.14

The Faculty of Old Age Psychiatry issued guidance with the British Geriatrics Society, the Royal College of General Practitioners and the Alzheimer’s Society on atypical antipsychotic use in BPSD patients.7 Since then, there have been reports that patients had their medication inappropriately withdrawn or switched.2 Furthermore, there were pharmaceutical issues such as polypharmacy with the prescribing of several antipsychotics concurrently or medications administered at high doses even exceeding the BNF limits or medications given for too long without reviewing the need or the dose.5 The use of antipsychotics appears to be associated with accelerated cognitive decline in people with AD.16

**Risk of death from prescribing antipsychotics**

The Food and Drug Administration (FDA) concluded that labelling for all atypical antipsychotics should include information regarding the increased risk of mortality in dementia. This was based on a meta-analysis of 17 placebo-controlled trials of four atypical antipsychotics. These trials showed the risk of death in the drug-treated patients was 1.6 to 1.7 times higher compared with placebo. The main causes of death appeared to be either cardiovascular or infection. Because of the results’ consistency, the FDA concluded that the effect was likely related to the common pharmacological effects of atypical antipsychotics, including those not included in the meta-analysis.17

Around 180 000 dementia patients are treated with antipsychotics in the UK each year, and up to 36 000 may benefit from the treatment. In terms of negative effects directly attributable to antipsychotics, use at this level equates to an additional 1800 deaths and 1620 cerebrovascular adverse events. The proportion of these prescriptions that would be unnecessary if appropriate support were available is unclear.18 There were significant changes in the management of BPSD using antipsychotics since the publication of the Banerjee report.18

**Are typical antipsychotics safer?**

Typical antipsychotics are relatively less effective at controlling schizophrenia’s negative symptoms. Two large observational and epidemiological studies examined the risk of death in patients taking typical antipsychotics. The first study included 27 259 subjects with a diagnosis of dementia and compared the risk for death with atypical antipsychotic versus no antipsychotic or typical antipsychotic. Typical antipsychotic
use showed a marginally higher risk of death compared with atypical antipsychotics. Another study included 37,241 subjects, prescribed either typical or atypical antipsychotics, and demonstrated that the risk of death with typical antipsychotics was comparable and possibly greater than atypical antipsychotics. Due to methodological limitations, the FDA highlighted that these results preclude any conclusion that typical antipsychotic medications had a greater risk of death. However, the FDA determined that the overall weight of evidence indicated that typical antipsychotics shared the increased risk of death observed for atypical antipsychotics.

The FDA notified health care professionals that typical and atypical antipsychotics were associated with an increased risk of mortality in elderly patients and required manufacturers to make safety label changes. The FDA and NICE recommend that physicians who prescribe antipsychotics should discuss the risk of increased mortality with their dementia patients, patients’ families and caregivers.

The Committee for Medicinal Products for Human Use concluded that there was ample evidence that typical antipsychotics were associated with an increased risk of death in dementia. The European Medicines Agency highlighted in addition to the FDA evidence that 10 further publications showed the risk of death associated with typical antipsychotics. Seven of them concluded that typical antipsychotics were associated with increased mortality, whilst three concluded that neither atypical nor typical antipsychotics were associated with increased mortality.

Licensing and guidelines in the UK
In the UK, there is no drug currently licensed specifically for BPSD management. Risperidone is licensed for short-term treatment (up to six weeks) of persistent aggression in moderate to severe AD and also for moderate Parkinson’s disease dementia (PDD). The only drug currently used for severe AD is memantine. Donepezil inhibits acetylcholinesterase with side-effects such as cardiac arrhythmia, gastrointestinal disturbances, pancreatitis, stroke, seizure, delirium, vivid dreams and insomnia. Memantine is a non-competitive NMDA antagonist as excessive glutamate excitotoxicity is implicated in dementia.

What evidence supports use of pharmacological alternatives?
Anti-dementia medications may have a beneficial effect on some behavioural symptoms. Cholinesterase inhibitors’ efficacy was demonstrated in several large RCTs as they reduce psychotic symptoms in dementia and can be a good alternative to antipsychotics, whilst behavioral symptoms in moderate to severe AD population were shown to improve with donepezil.

Current guidelines state that AD patients with non-cognitive symptoms and / or challenging behaviour may be offered a cholinesterase inhibitor if a non-pharmacological approach and antipsychotics were inappropriate or ineffective. However, for vascular dementia patients, the current guidelines do not recommend these medications except as part of clinical studies.

The Faculty of Old Age Psychiatry health technology appraisal recognised the adverse effects associated with antipsychotics and highlighted the benefits of cholinesterase inhibitors and memantine. It urged NICE to ensure these medications were not so restricted that they lead clinicians to consider the use of antipsychotics. The faculty suggested memantine should be recommended as a treatment option for patients with moderate to severe AD where there were prominent behavioural symptoms not managed by non-pharmacological means, and when alternative therapeutic options would involve high risk.

In NICE guidance, cholinesterase inhibitors are options for managing mild to moderate AD, while memantine is an option for people with moderate AD who cannot take cholinesterase inhibitors, and for severe AD. Patients on memantine were slightly less likely to develop agitation (12% versus 18% in the control group).

Anticonvulsants
Limited evidence suggests lamotrigine may be helpful for agitation and psychosis in dementia. Lamotrigine is an antiepileptic whose mechanism of action is linked to voltage-sensitive sodium-channel blockade in the neuronal membrane and inhibition of glutamate and aspartate release. Lamotrigine has good concordance, an acceptable side-effects profile (although a rash on initiation can influence adherence / continuation) and no worsening in the cognitive functions. Large clinical trials are required to confirm lamotrigine’s positive clinical outcome. Carbamazepine acts on sodium channels with demonstrated efficacy in agitation treatment. Gabapentin, a structural analogue of GABA, has shown efficacy in the management of behavioural
symptoms in AD. There is not enough evidence to support the use of valproic acid in the management of BPSD and the evidence even suggests that caution is needed.

**Selective serotonin re-uptake inhibitors**

Selective serotonin re-uptake inhibitors (SSRIs), including fluoxetine, citalopram, escitalopram, paroxetine and sertraline, are first line in depression treatment. SSRIs possess a relatively advantageous safety profile with similar efficacy to tricyclic antidepressants (TCAs) they inhibit serotonin re-uptake through 5-HT transporters; SSRIs lack significant cardiotoxicity (except citalopram) with less antimuscarinic, anti-adrenergic properties than TCAs. Citalopram has shown efficacy in AD patients in reducing agitation and caregiver distress in combination with psychosocial intervention. However, efficacy in treating depression in dementia is not fully supported. SSRIs can cause sexual dysfunction, G1 distress, bleeding complications and rarely serotonin syndrome. Serotonergic deficits in AD contribute to verbal and physical aggression, sleep disturbance, depression and psychosis. Common 5-HT receptor polymorphisms have been associated with visual hallucinations in AD, whilst aggression and psychosis in AD have been associated with 5-HT transporter polymorphisms.

Psychotic symptoms in AD are distinct from schizophrenia; 61% of patients experiencing hallucinations had only visual hallucinations. Delusions in dementia may result from misperceptions and impaired judgment. Consequently, delusions in AD may be attenuated by SSRIs’ anxiolytic effect. Citalopram was efficacious in the short-term treatment of BPSD in dementia. European data from countries including Switzerland, Germany and Austria suggested SSRIs as first-line in about 30% of BPSD patients. Trazodone, which blocks 5-HT2A and 5-HT2C receptors and inhibits serotonin transporter mechanisms, showed efficacy in controlling BPSD (a randomised controlled trial, a case series and other smaller studies). However, another study suggested that its efficacy was similar to placebo.

**Pharmacological treatment of sexually disinhibited behaviours**

There are no drugs currently licensed in the UK for sexually disinhibited behaviours; neuroleptics, anti-androgens, oestrogens, LHRH analogues, serotonergics and gabapentin are occasionally used off-licence. There is scarce evidence for neuroleptics. Citalopram and paroxetine, with a relatively safe profile, are associated with improvement in sexual aggression and disinhibition. Clomipramine, a TCA that inhibits serotonin and noradrenaline re-uptake, was effective. However, there are issues that need reviewing before recommending clomipramine as there is increased risk of falls and worsening confusion.

Cimetidine, an H2-antagonist, was associated with a reduction in libido and hyposexual behaviour in 14 out of 20 patients without remarkable side-effects. The other patients responded to combinations of cimetidine with ketoconazole, spironolactone. However the safety of using these combinations should be appropriately reviewed before they can be recommended.

Gabapentin showed a reduction in agitation and inappropriate sexual behaviour in vascular dementia and AD. Little is known about oestrogens and LHRH analogues, and there are no controlled studies for anti-androgens for the treatment of sexual disinhibition in patients with dementia, but they were used in sexual offenders. There are few reports on oestrogens for treating hypersexuality associated with dementia: more robust evidence is needed, and especially for oestrogen, as it is associated with cardiovascular-related deaths.

**Discussion**

Early data in a survey of old age psychiatrists showed that most of the respondents (95.5%) disagreed with the statement that antipsychotics should never be prescribed for patients with dementia and all reported that they prescribed antipsychotics for BPSD management. In light of the risk of death with conventional and atypical antipsychotics and their financial implications, antipsychotic medications should be avoided. This may apply after failure of non-pharmacological methods to manage BPSD, provided there is evidence for safer pharmacological alternatives. However, more robust studies are needed to validate the effectiveness and safety of alternative medications. There are challenges in the assessment and treatment of patients with BPSD. Consequently, a tailored care plan will be needed for each patient based on a person-centred approach and especially depending on an identifiable symptom that needs to be treated.

Withdrawal of antipsychotics improves functional and cognitive status in AD patients and can be achieved successfully in people relatively free from behavioural symptoms for at least three months. However, it is prudent to withdraw antipsychotics cautiously and gradually, except here there are specific and distressing medication side-effects. On the other hand, not everyone on atypical antipsychotics should have their drug stopped or changed as BPSD can persist in the long term and is
often resistant to treatment. Atypical antipsychotics can be continued if severe adverse consequences occur (or have occurred) when medications are discontinued or when no alternative treatment approach is suitable.

Is there a need for local protocols for the management of BPSD?

There is conflicting information from different sources such as academic literature, the pharmaceutical industry, guidelines, Trust policies, local experts and licensing authorities regarding the appropriate pharmacological management of BPSD.

National guidelines are expected to be influential and safe. An evidence-based approach takes account of the wider picture and is politically neutral with less risk of bias, but is time consuming. Local expert opinion can vary widely and may be influenced by local pharmaceutical exposure. Protocols for prescribing and monitoring need to be introduced. Some hospitals have developed local protocols with algorithms and flow charts suggesting first- and second-line pharmacological treatment in BPSD.

Algorithms use graphic representation for a scientific approach to a clinical problem. If wisely administered, algorithms have a role in patient care and cost-effectiveness. However, a valid criticism centres on their rigidity and the automatic approach they foster within the clinical field, if individual factors not considered, especially when such algorithms are poorly applied.25 Guidelines do not override health care professionals’ responsibility to make appropriate decisions depending on a patient’s circumstances, in consultation with the patient and/or their carer.1

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Declaration of interests

No conflicts of interest were declared.

References