Clinical Management of Behavioural and Psychological Symptoms of Dementia

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Behavioural and psychological symptoms of dementia (BPSD) occur at some point in over 90% of patients with dementia. Behavioural symptoms are identified on the basis of observation of patients, and include physical aggression, screaming, restlessness, agitation, wandering, culturally inappropriate behaviours, and sexual disinhibition. Psychological symptoms are mainly assessed based on interviews with patients and relatives, and include anxiety, depression, hallucination and delusion. No matter in what form do the BPSD appear, the first step is a careful search for the precipitants or stimulants of disruptive behaviours. Environmental triggers such as temperature, noise and bad smell, basic needs such as hunger or thirst, common medical problems such as pain and constipation, or social triggers such as change or loss of caregiver, are precipitating factors to be watched out for. The first approach to management of BPSD should therefore be environmental modification and behavioural interventions. When non-pharmacological interventions are found to be ineffective, drug therapy is often tried. A wide range of medications have been used, including anti-dementia drugs (cholinesterase inhibitors and NMDA receptor agonist), antipsychotics, antidepressants, anxiolytics and anticonvulsants/mood stabilisers (Table 1). The type of medications used usually depends on the likely antecedent of the behaviour, for example, antidepressants and anxiolytics if the patient is pacing around with increasing anxiety, or antipsychotics if the patient is responding to voices.

Cholinesterase Inhibitors

Cholinesterase inhibitors are currently the drugs of choice for treating patients with mild-to-moderate Alzheimer’s disease. Three types of cholinesterase inhibitors are available in Hong Kong.

Donepezil

The drug with the greatest impact so far on the treatment of Alzheimer’s disease has been donepezil. The starting dosage is 5mg nocte, increased to 10mg nocte after a month if necessary. Peripheral side-effects, which include diarrhoea, nausea, vomiting, insomnia, muscle cramps and anorexia, are generally of mild intensity and transient, resolving during continued donepezil treatment. Caution should be used in patients with asthma, renal disease, cardiac disease, epilepsy, and prior upper gastrointestinal bleeding.

There is now clear evidence emerging from clinical practice that the behavioural or non-cognitive symptoms of dementia are improved with donepezil treatment.

Alzheimer’s disease patients with more marked delusions, agitation, depression, anxiety, apathy, disinhibition and irritability are most likely to improve when treated with donepezil.

Rivastigmine

Rivastigmine has shown efficacy in treating behavioural disturbances in patients with a wide range of dementias, including Alzheimer’s disease, vascular dementia, frontotemporal dementia, mixed dementia, Lewy body dementia, Parkinson’s disease with dementia, and schizophrenia with dementia. The behaviour domains that most consistently showed improvement were apathy/indifference, anxiety, delusions and hallucinations. There is also a substantial decrease in the use of antipsychotics for BPSD by patients taking rivastigmine, compared with patients not taking cholinesterase inhibitors.

A large randomised controlled trial has compared the efficacy of donepezil and rivastigmine in moderate to moderately severe patients with Alzheimer’s disease over a 2-year period. Both cholinesterase inhibitors had comparable effects on cognitive and behavioural measures, and rivastigmine was superior on measures of activities of daily living and global functioning. A local study showed that rivastigmine significantly improved BPSD in Chinese patients with Alzheimer’s disease, particularly in delusions, depression/dysphoria, disinhibition, irritability/lability, aberrant motor behaviour, and night-time behaviour disturbance.

Rivastigmine was also shown to be useful in Lewy body dementia. Lewy body dementia is a common form of dementia in the elderly, characterised clinically by fluctuating cognitive impairment, visual hallucinations and parkinsonism. Patients with Lewy body dementia taking rivastigmine were significantly less apathetic and anxious, and had fewer delusions and hallucinations than controls.

Because of its short half-life, rivastigmine has to be given twice daily. Titration should start at 1.5mg BD, increased to 3mg BD after a minimum of 2 weeks, aiming at an effective maintenance dose of 3mg BD to 6mg BD.

Galantamine

In randomised, double-blind, placebo-controlled trials of up to 6 months’ duration, galantamine consistently produced a broad spectrum of beneficial effects on cognitive and non-cognitive symptoms. Patients’ cognition, global function and abilities to perform activities of daily living were maintained, the emergence of behavioural symptoms was postponed and apparent
reductions in caregiver burden were seen.11-14

In a recent randomised, double-blind, placebo-controlled trial, the effects of galantamine were investigated in patients with probable vascular dementia or Alzheimer’s disease combined with cerebrovascular disease.15 Galantamine showed greater efficacy than placebo in cognitive function, activities of daily living and behavioural symptoms in this group of patients.

Starting at 4mg BD, galantamine can be increased to 8mg BD after 4 weeks and then to 12mg BD after another 4 weeks if tolerable and having clinical benefit. Gastrointestinal side effects are infrequent and mild, and can be minimised using slow dose-escalation regimen.

NMDA Receptor Antagonist

Memantine

Memantine is approved for the treatment of moderate to severe Alzheimer’s disease, and is the first anti-dementia drug to be available for this group of patients with advanced disease.

The recommended dosage of memantine is 10mg BD. Dosage reduction is needed in those with moderate renal impairment, and it is not recommended in patients with severe renal impairment. Caution should be exercised in patients with recent myocardial infarction, uncompensated congestive heart failure, uncontrolled hypertension or seizures. Adverse events were usually mild, including diarrhea, insomnia, dizziness, headache, hallucinations, agitation and urinary incontinence.

Combining the data from two randomised controlled trials (RCTs) on the behavioural symptoms in Alzheimer’s disease, memantine was found to be particularly effective in the agitation/aggression domain in the Neuropsychiatric Inventory.16 Memantine can also be safely combined with cholinesterase inhibitors such as donepezil and rivastigmine as an add on therapy. Memantine has been shown to be superior in combination therapy with donepezil, in patients with moderate to severe Alzheimer’s disease, when compared to using donepezil alone.17,18

Antipsychotics

Delusions and hallucinations are very common in all stages of dementia, and they often respond well to low dose antipsychotics treatment. Conventional antipsychotics such as haloperidol, trifluoperazine, chlorpromazine and thioridazine have generally fallen out of favour for the treatment of BPSD, because of their side effects such as extrapyramidal symptoms, tardive dyskinesia, falls and orthostatic hypotension, anticholinergic and cardiac side effects. Currently there is a preference for newer antipsychotics such as risperidone, olanzapine, quetiapine and aripiprazole which are better tolerated by the elderly, although none of them has an approved indication for the treatment of BPSD. These atypical antipsychotics produce fewer extrapyramidal side effects, less tardive dyskinesia and fewer adverse cognitive effects, although they are more expensive than the conventional antipsychotics.

Atypical antipsychotics have been extensively studied in the treatment of BPSD. The effect size is only modest, with 20% better response rate than placebo in reducing agitation and psychosis.19 RCTs showed that the atypical antipsychotics risperidone, olanzapine, quetiapine and aripiprazole are beneficial in terms of reduced neuropsychiatric symptoms,20 and that risperidone and olanzapine significantly reduce aggression.21,22 Another recent RCT showed that aripiprazole significantly improved psychotic symptoms and agitation in patients with Alzheimer’s disease.23 Preliminary studies showed that another atypical antipsychotics amisulpride is useful in controlling agitation, and is as effective and tolerable as risperidone in the treatment of BPSD.24,25

There are major controversies over the use of atypical antipsychotics for BPSD in the recent years. Data from four RCTs involving 1230 patients with dementia have raised concerns about the increased risk of cerebrovascular adverse events including stroke (two to three times), accelerated cognitive decline, and mortality (1.7-fold increase) with the use of atypical antipsychotics in patients with dementia.26 Subsequently, regulatory authorities such as the European Drug Agency, Committee for the Safety of Medicine (CSM) in the UK and the FDA have issued advisory standings that all atypical antipsychotics should no longer be prescribed for the treatment of BPSD. However, further studies found a much smaller risk. For example, a systematic review of 15 RCTs, including a total of 3353 patients, suggested that only a small increase in risk of death was associated with the use of atypical antipsychotics as compared with placebo.27 Subsequent studies found that the increased cerebrovascular risk is probably a class effect, with conventional antipsychotics also involved.28 The latest evidence is provided by CATIE-AD, the first head-to-head, prospective, randomised, double-blind, placebo-controlled effectiveness trial of antipsychotic therapy in Alzheimer’s disease. In this uniquely designed study with prescribing pattern similar to the real-world clinical situation, there were no observed differences in the rates of stroke or sudden death between the groups receiving atypical antipsychotics (olanzapine, quetiapine, risperidone) and placebo.29

Although caution is undoubtedly required with the use of these drugs, advising absolutely against them creates great difficulties for the management of patients with severe behavioural disorders, especially in the absence of better proven alternatives.30 Clinical judgement and decisions based on individual medical needs and comorbidity, consideration of alternative treatments, and a thorough discussion of the potential benefits and risks with the patient and the relatives or caregivers are recommended.31 The risk factors for cerebrovascular diseases, including previous history of stroke or transient ischaemic attack, hypertension, diabetes mellitus, smoking and atrial fibrillation, are to be considered before prescription. Treatment should be time limited and regularly reviewed every 3 months.

Antidepressants

Making the diagnosis of depression in a demented elderly can be very difficult, because of their speech and comprehension disabilities. Careful monitoring of the
patient's facial expression, collateral information from the caregiver regarding tearful episodes, eating and sleeping patterns, can aid in the diagnosis. Irritable mood and somatic symptoms without biological explanations are also common presentations of depression in the demented elderly.

Selective Serotonin Reuptake Inhibitors (SSRIs) and other newer antidepressants are the first choice for reasons of tolerability. SSRIs such as fluoxetine, sertraline, paroxetine, citalopram and escitalopram, when compared with the older generation tricyclic antidepressants (TCAs), have the advantages of having less sedation, fewer anticholinergic effects, low cardiotoxicity, no postural hypotension, and safety in overdose. Side effects such as gastrointestinal upset and headache are generally dose-related and time-limited. Other useful newer antidepressants are venlafaxine (SNRI: Serotonin Noradrenaline Reuptake Inhibitors) and mirtazapine (NaSSA: Noradrenergic and Specific Serotoninergic Antidepressant).

Depression may not persist for a long duration in demented patients, so it is reasonable to consider tapering the antidepressant after 6 months to 1 year after the clinical response is achieved and maintained.

**Anxiolytics**

Anxiety is a symptom of depression, but it can also be induced by hallucinations and delusions. Anxiety in turn can lead to agitation and restlessness, repetitive vocalisation, insomnia, and resistive behaviour. Anxiety can be minimised by a gentle, calm approach by caregivers, by maintaining eye contact, and by explanation to the demented elderly of what is being done. Gentle distraction and involvement in activities are usually effective in reducing anxiety. 32

Sedative-hypnotics are indicated for the acute treatment of anxiety syndrome, insomnia, non-specific agitation in the absence of psychosis and for time-limited sedation (for example before a bath or procedures), when behavioural and environmental management are not effective. Sedative-hypnotics (mostly benzodiazepines) are generally less efficacious than antipsychotics for BPSD, and initial improvement may be lost after prolonged use due to tolerance. Common side effects in the elderly are increasing confusion, paradoxical rage or agitation, daytime sedation, dizziness and falls, and benzodiazepine dependence syndrome. For these reasons, one should try to limit the use of anxiolytics to short term (4 to 8 weeks), and on a prn basis.

**Anticonvulsants / Mood Stabilisers**

Use of anticonvulsants for agitation in dementia was originally advocated on the basis of extrapolation from reports that they reduced agitation, aggression, irritability and impulsivity across a wide range of other clinical disorders. For carbamazepine, there are only 2 RCTs for agitation in severely demented subjects. 22 Available data suggest that carbamazepine is safe and effective in treatment of agitation, at least in one of the trials and in the short term. However, rare toxicities such as hepatitis, blood dyscrasias and the fatal Stevens-Johnson syndrome may limit its prescription in the elderly. For sodium valproate, only 3 RCTs are available, showing no difference in treatment of depression and anxiety symptoms when compared to placebo group. 22 When prescribing anticonvulsants, regular blood level monitoring of anticonvulsants should be scheduled. When used for treating agitation, these drugs may be effective in blood concentrations lower than those required for control of seizures.

**Conclusion**

Pharmacological interventions can complement non-pharmacological interventions in the treatment of BPSD. Because of their beneficial effects on cognitive and behavioural symptoms and in functional improvement, cholinesterase inhibitors are now commonly prescribed for patients with mild-to-moderate Alzheimer's disease. For pharmacological treatment of BPSD, a realistic goal is a reduction in the frequency or severity of the symptoms rather than a complete remission. Most behavioural problems are only present through a portion of the natural history of the dementia, so it is important to reassess and stop unnecessary medications such as antipsychotics and anxiolytics at a later stage. Dosing should be kept to one to two times per day as the memory function of the demented patient is impaired. The golden rule of prescribing in the elderly "start low and go slow" must also be remembered.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Daily dose</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>25 - 100 mg</td>
<td>QD</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10 - 40 mg</td>
<td>QD</td>
</tr>
<tr>
<td>Citalopram</td>
<td>10 - 40 mg</td>
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<td>Venlafaxine XR</td>
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</tr>
<tr>
<td>Mirtazapine</td>
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<tr>
<td><strong>Anxiolytics</strong></td>
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<td></td>
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<tr>
<td>Lorazepam</td>
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<td>Alprazolam</td>
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<tr>
<td><strong>Anticonvulsants/mood stabilisers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>400 - 600 mg</td>
<td>BD</td>
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<tr>
<td>Sodium valproate</td>
<td>400 - 600 mg</td>
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References


