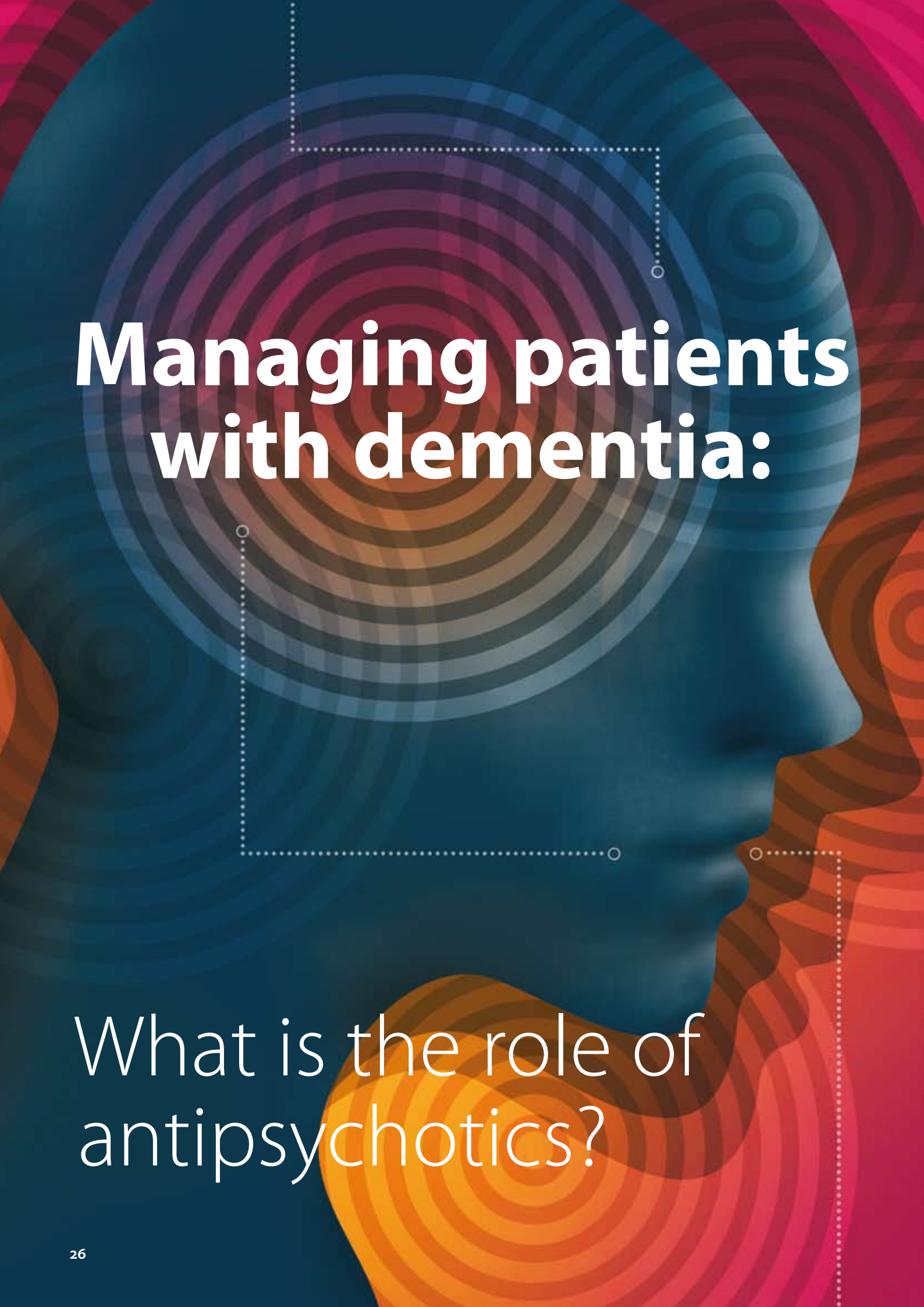

Managing patients with dementia:

What is the role of antipsychotics?

Concerns have been raised, both in New Zealand and internationally, about the increasing off-label use of antipsychotics, and their safety profile in older people. Antipsychotics should not be considered in older people with dementia before non-pharmacological treatment strategies have been trialled. The potential benefit of antipsychotics needs to be weighed against the significant likelihood of adverse effects. The choice of antipsychotic is also important and needs to take into account both relative efficacy and safety. Antipsychotics are only useful for specific behaviours associated with dementia, such as psychosis and agitation. If antipsychotics are prescribed, response to treatment and adverse effects must be carefully monitored.

The behavioural and psychological symptoms of dementia

The behavioural and psychological symptoms of dementia (BPSD) are defined as symptoms of disturbed perception, thought, mood or behaviour in a person with dementia, which are not due to another major neuropsychiatric disorder, such as a major depressive episode.[1] Almost all people with dementia experience inappropriate behavioural and psychological symptoms at some point during their illness. This can cause significant stress to family and caregivers and result in institutionalisation. As there is no cure for dementia, appropriate treatment of BPSD can have a significant impact on the quality of life of the patient, their families and caregivers.

There is concern that antipsychotics are being over-prescribed to control inappropriate behaviour in people with dementia.[2] The first approach to managing BPSD is to try to understand why the behaviour is occurring, and, where possible, control for these factors.

Although the evidence base for non-pharmacological treatments of BPSD is not strong, there are generally less risks associated with these interventions and they should always be considered first. Non-pharmacological interventions should be tailored to the individual patient and the target behaviour(s) and the impact carefully monitored.

Identify target behaviours

There are a variety of challenging behaviours and symptoms that may present in older people with dementia. As different behaviours are often best managed using different approaches, it is critical to first decide which behaviours are being targeted for management. Identifying target behaviours also allows the response to treatment to be more accurately monitored.[2]

Common target problems and behaviours observed in elderly people with dementia or other mental illnesses include:[2]

- Calling out
- Aggression
- Agitation
- Hallucinations and illusions
- Delusions
- Wandering
- Depression
- Elevated mood
- "Sundowning", e.g. increased agitation in the late afternoon
- Insomnia
- Apathy/lack of motivation
- Extreme anxiety
- Resistance or unease towards carers
- Intrusive behaviours
- Inappropriate sexualised behaviour
- Inappropriate urination or defaecation
- Other inappropriate social behaviours

 Record the target problem(s) and the response to treatment in the patient's notes.

Assess underlying causes and contributing factors

Medical and environmental factors can often precipitate or exacerbate BPSD. Patients presenting with BPSD should be assessed to exclude reversible causes, minimise precipitating factors, and to develop an individualised plan.

Assessment should include consideration of the following factors:[3]

- Are the symptoms explained by another psychiatric condition such as depression or delirium?
- Is the patient taking any medicines that may be causing or contributing to the symptoms?
- Is the patient in otherwise good physical health? Is there a possibility of undetected pain, infection, constipation or discomfort?
- Are there any factors in the patient's living environment, i.e. their home/care facility, or unmet personal needs which may be exacerbating behaviours?

Differential diagnosis: The 3Ds

Depression and delirium can also be associated with BPSD-like symptoms, therefore it is important to distinguish dementia from these conditions (referred to as the 3Ds). Differential features of the 3Ds are presented in Table 1, but there is considerable overlap and the 3Ds often co-exist. Severe depression can present as a dementia-like illness (pseudodementia). Delirium can be caused by infections, drug toxicity, alcohol withdrawal and metabolic disturbances.

Medicines that could precipitate or worsen BPSD

If an older person presents with new or worsening BPSD, current medicines should be excluded as a possible precipitant.

Medicines which can be associated with cognitive impairment include:[5]

- Anticholinergics, e.g. amitriptyline, oxybutynin
- Anticonvulsants, e.g. carbamazepine, phenytoin
- Lithium
- Systemic corticosteroids, especially high doses
- H2 antagonists, e.g. ranitidine
- Some antibiotics, e.g. ciprofloxacin, norfloxacin, metronidazole, clarithromycin

Table 1: Differential features of the 3Ds: delirium, dementia and depression[4]

Feature	Delirium	Dementia	Depression
Onset	Hours to days Usually sudden, often in the evening	Months to years Chronic and generally insidious	Weeks to months Sometimes relatively abrupt and coinciding with life changes, but may also be insidious and not clearly linked to life events
Duration	Hours to less than one month, rarely longer	Months to years	Months
Progression	Abrupt, fluctuating	Slow but generally steady	Variable and uneven
Thinking	Disorganised, slow, incoherent	Paucity of thought, poor judgment; words hard to find	Intact with themes of helplessness, generally negative
Memory	Impaired, sudden	Impaired	Selective or patchy
Sleep	Nocturnal confusion	Often disturbed; nocturnal wandering	Reduced sleep with early morning wakening, or may oversleep
Awareness	Reduced	Clear	Clear
Alertness	Fluctuates; lethargic or hypervigilant	Generally normal	Normal
Attention	Impaired, fluctuates	Generally normal	Minimal impairment but easily distracted

- Analgesics, particularly opioids
- Anti-Parkinson's medicines
- ACE inhibitors
- Digoxin

Undetected medical conditions

The following medical conditions can potentially cause, contribute to or mimic BPSD and should be considered:[3]

- Pain (see opposite)
- Infection (especially urinary tract infection)
- Dehydration or hyponatraemia
- Constipation
- Urinary retention
- Anxiety
- Fatigue
- Hearing/visual impairment
- Poor dental health

Personal or environmental factors that can cause or exacerbate BPSD

Problems in the design and configuration of the patient's home or residential facility can cause or exacerbate restlessness, frustration, anxiety and disorientation. Simple changes in the environment can be beneficial and may be worth discussing with the patient's family, carer or residential care manager, including:[3, 8]

- Promote a calm, tranquil environment, i.e. avoid overstimulation
- Ensure that the patient's home/room is at a comfortable temperature
- Ensure easy access to the toilet
- Have well lit surroundings
- Use signs and memory aids for objects within the home that the patient commonly uses
- Improve time orientation, e.g. prominent calendar/clock
- If the patient is in a residential care facility, make their environment as "home-like" and reassuring as possible, by ensuring the patient is surrounded by their personal belongings, including culturally significant items
- Encourage involvement in group activities to prevent boredom and loneliness
- If possible, ensure consistency of carers
- Ensure the patient has privacy

Encouraging people with dementia to participate in activities which are meaningful and enjoyable to them may improve their sense of wellbeing and communication and lead to

Untreated pain may be a cause of BPSD

Pain is estimated to occur in up to 83% of patients with dementia.[6] It is often poorly recognised and undertreated due to the patient's difficulty in communicating their needs. Symptoms of BPSD, e.g. calling out, agitation and restlessness, can be due to undertreated pain.

Regularly ask the patient whether they have any pain. Keep questions simple, e.g. "is it sore"? or "does it hurt"? It may be necessary to observe breathing patterns, facial expression or vocalisations to assess pain in a patient with dementia. There are several tools available to help establish if a patient with cognitive impairment is in pain, if they cannot tell you in words. A New Zealand study found that the Pain Assessment Scale for Seniors with Limited Ability to Communicate (PACSLAC) was easily used by caregivers, and resulted in increased use of "as needed" analgesic medicines and reduced levels of caregiver stress.[7]

PACSLAC is available from: **www.rgpc.ca**

reductions in BPSD. This might include exercising, gardening, music, dancing, art or interactions with a pet. There is some limited evidence that aromatherapy can improve symptoms of BPSD and increase quality of life in people with dementia.[9]

Behaviour management

Behaviour management is defined as a structured intervention, usually carried out by family or other caregivers, under the supervision of a professional with expertise in this area. This might involve providing reinforcement for increased social activity or removing reinforcement for attention seeking behaviour. Behavioural management involving scheduling enjoyable events or engagement in problem-solving activities has been shown to improve symptoms of depression in people with dementia.[10]

Inappropriate sexual behaviour can be particularly challenging to address. Strategies include separating the patient from a person who might be a trigger for the behaviour and distraction with other activities, e.g. craft work to occupy the hands.[11]

Antipsychotics are second-line

Antipsychotics may be considered for treating aggression, agitation or psychotic symptoms. They are not useful for wandering, shouting, touching or social withdrawal.

Antipsychotics are only appropriate for patients with BPSD if aggression, agitation or psychotic symptoms are causing severe distress or an immediate risk of harm to the patient or others.[8, 10] Unless emergency treatment is required, non-pharmacological treatment should always be tried first and continued concurrently with antipsychotics.

Antipsychotics are not recommended for patients with mild to moderate BPSD,[10] and are not usually effective for other symptoms such as wandering, social withdrawal, shouting, pacing, touching or incontinence.[12] Antipsychotics do not appear to improve overall functioning, care needs or quality of life in patients with dementia.[13]

If an antipsychotic is prescribed, it should be given on a trial basis, and response and adverse effects regularly reviewed. An appropriate trial of an antipsychotic for patients with aggression or agitation is up to four weeks and up to three months for patients with psychotic symptoms, e.g. delusions or hallucinations.[2] If possible, antipsychotics should not be used long-term for patients with dementia.

Antipsychotics can modestly improve BPSD in some patients

Antipsychotics are only modestly effective in managing BPSD, and the level of effectiveness varies between patients. They should not be regarded as a "cure" for BPSD. Traditionally, older antipsychotics (referred to as typical antipsychotics) such as haloperidol were used to manage symptoms in patients with dementia. Newer, atypical antipsychotics, such as risperidone, olanzapine, quetiapine and aripiprazole are now used. They are no more effective than typical antipsychotics for BPSD, but are regarded as being better tolerated and safer (in terms of adverse effects) to use in older people.[2]

A meta-analysis which measured improvement in psychosis (e.g. delusions and hallucinations) and agitation (e.g. aggression, excitability, oppositional behaviours or excessive motor activity) with use of atypical antipsychotics found that the overall observable change was a 35% improvement in behaviour compared to baseline.[14] A 30% improvement in behaviour is regarded as the minimum clinically observable change.[14] Risperidone, olanzapine and aripriprazole had a small, but statistically significant, beneficial effect on symptoms. The effect of quetiapine was not significant.[14] In contrast, a 2011 meta-analysis found that patients using quetiapine had a statistically significant improvement in BPSD, but the improvement was of questionable clinical significance.[15]

Which antipsychotic to choose for BPSD?

The choice of antipsychotic is based on their relative efficacy and adverse effects, along with subsidy status. Common adverse effects associated with all antipsychotics include sedation, dizziness, postural hypotension and confusion, which may increase the risk of falls in older people.[5, 16] The anticholinergic properties of antipsychotics can worsen cognition or cause delirium. Extrapyramidal adverse effects occur more commonly with typical antipsychotics, but can occur with risperidone even at relatively low doses. Rarely, tardive dyskinesia can occur. Metabolic changes, e.g. significant weight gain, hyperglycaemia and effects of increased prolactin (e.g. galactorrhoea), have also been associated with antipsychotics, but this is not observed to occur as frequently in older people. Many of these effects can be potentiated by interactions with other medicines and co-morbid conditions.[16]

Risperidone is the most extensively studied antipsychotic for use in BPSD, and is the only atypical antipsychotic approved for this use in New Zealand. Risperidone is, therefore, the first-line choice when an antipsychotic is prescribed for BPSD.[14]

If risperidone is not tolerated or not appropriate, then other antipsychotics may be considered in some patients. Other atypical antipsychotics are not approved for use in BPSD in New Zealand, so are regarded as being used "off-label" for this indication. Table 2 shows a comparison of adverse effects for antipsychotics commonly used in the treatment of BPSD.

For further information about off-label prescribing, including prescriber obligations, see: "Unapproved medicines and unapproved use of medicines: keeping prescribers and patients safe", BPJ 51 (Mar, 2013).

Quetiapine appears to be increasingly used in older people, and evidence from cohort studies suggests it is safer than other antipsychotics (including risperidone) in terms of mortality risk, but it may not be as effective.[14, 15] Quetiapine at low doses (< 100 mg/day) is generally well tolerated in older people.

Olanzapine has been shown to be modestly effective for treating agitation, however, the evidence is not as robust as it is for risperidone.[18] Olanzapine is associated with more metabolic adverse effects, including rapid and significant weight gain, dyslipidaemia and type 2 diabetes, than other antipsychotics.[14, 16]

Aripiprazole has been shown to be modestly effective for symptoms of agitation and psychoses associated with BPSD.[18] However, it is not subsidised for this use as a Special Authority is required for subsidised prescription and the criteria do not cover BPSD. If aripiprazole is being considered, this should be discussed with a Psychiatrist or Geriatrician.

Haloperidol has traditionally been used for BPSD and does not differ significantly in effectiveness from atypical antipsychotics. However, it should generally be avoided in older people given the high risk of extrapyramidal adverse effects and increased mortality compared to atypical antipsychotics.[2, 16] Low-dose haloperidol has a restricted place in the short-term management of the acute symptoms of delirium (except in people with Parkinsonism of any cause).

The newer antipsychotics **amisulpride**, **paliperidone** (not subsidised) and **ziprasidone** (not subsidised for this indication) do not yet have an evidence base to support their use in BPSD.

Table 2: Comparative risk of adverse effects of antipsychotics commonly used wfor BPSD.[16, 19]

	Risperidone	Quetiapine	Olanzapine	Aripiprazole	Haloperidol
Anticholinergic effects	+	+	+	•	+
Dyslipidaemia	++	++	+++	•	+
Extrapyramidal symptoms	++	•	+	+	+++
Hyperprolactinaemia	+++	+	+	•	+++
Neuroleptic malignant syndrome	+	+	+	+	++
Postural hypotension	++	++	+	+	+
Prolonged QT interval	+	+	+	+	++
Sedation	+	++	++	+	+++
Seizures	+	+	+	+	+
Sexual dysfunction	+	+	+	+	+++
Type 2 diabetes	+	+	++	+	+
Weight gain	++	++	+++	•	++

• = rare, + = lower risk, ++ = medium risk, +++ = higher risk

Lewy Body dementia and dementia associated with Parkinson's disease

Approximately 10% of people with dementia have Parkinson's disease or significant Parkinsonian symptoms.[20] Some of these people have Lewy Body dementia. Core symptoms of Lewy Body dementia include complex visual hallucinations, fluctuating cognitive impairment and Parkinsonism that is neither stroke nor drug-induced. It is recommended that a Psychiatrist or Geriatrician is consulted before considering prescribing any medicines for BPSD in people with Lewy Body dementia.

Typical antipsychotics such as haloperidol should not be used in people with Lewy Body dementia or dementia associated with Parkinson's disease as they can cause dangerous extrapyramidal symptoms. There is also an increased risk of neuroleptic malignant syndrome, which is a life-threatening disorder induced by dopamine antagonists, characterised by hyperthermia, hypertonia ("lead pipe" rigidity in all muscle groups), changes in mental state, hyporeflexia and haemodynamic instability.[21] Atypical antipsychotics, especially olanzapine, are also best avoided, as they can result in severe sensitivity reactions (e.g. marked extrapyramidal effects, confusion, autonomic instability, falls and increased mortality).[20] Quetiapine may be used at low doses with extreme caution, in consultation with a Geriatrician or Psychiatrist, if cholinesterase inhibitors and non-pharmacological treatments have failed.[22]

Safety concerns with antipsychotics in older people

Antipsychotics are associated with additional serious safety concerns when used in older people with dementia, such as an increased risk of stroke and overall mortality. When considering antipsychotic treatment, these risks need to be balanced against the risk of injury (due to BPSD) for individual patients.

Increased risk of cerebrovascular events

Atypical antipsychotics, such as risperidone and olanzapine, have been associated with an increased risk of cerebrovascular adverse events, such as stroke, in older people with dementia, particularly those with more advanced dementia. It is not known what the exact mechanism for this association is. There is evidence to suggest that the risk of stroke may be greatest in the first weeks of use of an atypical antipsychotic, and people with a past history of cerebrovascular events are particularly at risk.[23] The risk of stroke may not return to baseline until six months after a patient ceases antipsychotic treatment (depending on the length of treatment).[24] Typical antipsychotics are also associated with an increased risk of stroke, but there is some evidence that this risk is less than that with atypical antipsychotics.[24] Antipsychotics should be prescribed with caution in elderly people with dementia who have an increased cardiovascular risk or personal or family history of cerebrovascular events.

An analysis of trials found an increased odds ratio of 2.13 for cerebrovascular adverse events in people taking antipsychotics for dementia. This risk was especially high with risperidone (odds ratio 3.43).[25] Another systematic review and meta-analysis also found that risperidone was associated with an increased risk of stroke (odds ratio 3.12).[14] The number needed to harm was 53.[14] A comparative study found that there was no difference in risk of stroke between patients taking risperidone and patients taking olanzapine, i.e. suggesting that olanzapine has the same increased risk.[17] Patients taking quetiapine had a smaller risk of cerebrovascular adverse events than those taking olanzapine.[17]

Increased mortality

Atypical antipsychotics have been associated with an increased overall mortality rate in older people with dementia. In 2005, the United States Food and Drug Administration (FDA) stated that the risk of mortality was increased 1.6 -1.7-fold in patients treated with atypical antipsychotics for BPSD.[26] A subsequent meta-analysis also found a similar mortality rate with atypical antipsychotics.[4] For every 87 patients treated with an antipsychotic for dementia, one patient will die.[14]

The risk of death is significantly lower for quetiapine compared to risperidone or olanzapine, which in turn has a lower risk of death than haloperidol.[27, 28] The highest increase in mortality is in the first four months of treatment and in the first 30 days for haloperidol, although study participants receiving haloperidol may have been more unwell, and had received the medicine during an inpatient hospital admission.[27] This finding contrasts to that of the DART-AD study which found that the risk of death may increase with long-term treatment.[29]

The most common conditions associated with cause of death appear to be pneumonia (see below) or cardiac failure or arrest.[30] Antipsychotics prolong the QT interval, which can result in ventricular tachyarrhythmia and sudden cardiac death. The risk of cardiac death increases with increasing dose, and the risk is similar between typical and atypical antipsychotics.[31] The risk is no longer elevated when use of antipsychotics ceases.[31] Antipsychotics should be prescribed with caution in patients taking other medicines which prolong the QT interval, e.g. erythromycin, citalopram, venlafaxine.

A full list of medicines with the potential to cause prolonged QT interval is available from: **www.qtdrugs.org**

Potential increased risk of pneumonia

Population based studies have suggested that there is an increased risk of pneumonia in older people (with or without dementia) treated with antipsychotics. The risk is thought to be greater with atypical antipsychotics, and the risk may be highest during the first week of treatment.[32]

It is not known how antipsychotics increase the risk of pneumonia, however, dysphagia (due to H1 receptor blockade), dry mouth (due to the anticholinergic effect), sedation (facilitating aspiration pneumonia) and direct or indirect effects on the immune system have been suggested as possible mechanisms.[32]

Guidance for prescribing antipsychotics in elderly people

Obtain informed consent

Before prescribing an antipsychotic for BPSD, a full discussion should take place regarding the possible benefits and risks of treatment, including the increased risk of stroke and all-cause mortality in people with dementia.[2, 10] Many patients

Table 3: Recommended starting and maintenance doses for antipsychotics in older people[2, 5]

Medicine	Dose	Comments
Risperidone	0.25 – 0.5 mg initially, titrated to maximum 2 mg daily in patients with dementia (6 mg daily may be tolerated in other patients), in one or two divided doses	Only approved atypical antipsychotic for BPSD. At higher doses it may behave more like a typical antipsychotic in terms of a higher incidence of extrapyramidal effects.
Quetiapine	12.5 mg initially, titrated to maximum 100 mg daily in patients with dementia (300 mg daily may be tolerated in other patients), in two or more divided doses	Current evidence suggests limited effectiveness for BPSD, although possibly safer in terms of mortality risk
Olanzapine	2.5 mg initially, titrated to maximum 10 mg daily (less in patients with dementia), in one or two divided doses	May be modestly effective for treating agitation, but generally not recommended in people with dementia. Associated with greater comparative risk of adverse metabolic effects.
Aripiprazole	5 mg – 10 mg daily	Not subsidised for use in BPSD
Haloperidol	0.25 mg, twice daily, titrated up to 3 mg daily	Effective for the short-term management of the acute symptoms of delirium (except in people with Parkinsonism of any cause). Not recommended for long-term use. High risk of extrapyramidal adverse effects and increased mortality compared to atypical antipsychotics.

with dementia will lack competency to decide on their own treatment, therefore the person legally responsible for the patient's medical decisions must be given information that is easily understood so they can make an informed decision.[2]

"Start low and go slow"

If a trial of antipsychotic treatment is considered necessary, the starting dose should be as low as possible (Table 3). The starting dose can be divided or timed according to the behaviour, e.g. a lunchtime dose for patients exhibiting increased agitation towards the end of the day ("sundowning").

The dose can be slowly increased at no less than weekly intervals, depending on response. High doses should be avoided, and treatment should be stopped if it has not significantly improved the target behaviour.[2]

Monitor closely for adverse effects

Older people are especially vulnerable to the adverse effects of antipsychotics, and these may outweigh any benefits. Adverse effects are generally dose-related and can be minimised by keeping the dose as low as possible.

Monitor for:

- CNS depression – sedation, increased confusion or cognitive impairment. Concurrent medicines may worsen effects, including benzodiazepines, opioids, antihistamines, antidepressants, anti-Parkinson's medicines.
- Anticholinergic effects – dry mouth, constipation, urinary retention, blurred vision, delirium. Concurrent medicines may worsen effects, including tricyclic antidepressants, oxybutynin and opioid analgesics.
- Dizziness and postural hypotension – increases risk of falls. Concurrent medicines may worsen effects, including antihypertensives, diuretics, SSRIs (causing hyponatraemia).
- Extrapyramidal effects – dyskinesias, dystonias
- Metabolic changes – monitor weight and monitor HbA_{1c} at baseline, then every three months in year one (or fasting glucose monthly for first three months in patients at high risk)*, and annually for subsequent years
- Infection – in particular urinary tract infections and pneumonia

Regularly review the need for continuing treatment

Gradual dose reduction and eventual withdrawal should be tried every three months. There have been very few studies done to measure the effectiveness of antipsychotics for BPSD longer than three months. In addition, BPSD may be temporary. A recent Cochrane review concluded that antipsychotics could be routinely withdrawn without adversely affecting behaviour, in all patients apart from those with severe symptoms.[33]

Longer-term use of antipsychotics is reported to be associated with a higher risk of relapse of symptoms. A study found that in patients who had been treated with risperidone for BPSD for four to eight months, discontinuation was associated with an increased risk of relapse.[34] The risk of recurrence of symptoms may also be higher in people with previously severe symptoms and if discontinuation has caused recurrence before.

Withdrawal of antipsychotics should be done gradually, e.g. by reducing the dose by 50% every two weeks then stopping after two weeks on the minimum dose. Withdrawal may be slower if the antipsychotic has been prescribed for a longer period of time. Monitor for recurrence of target behaviours or the emergence of new symptoms.

Challenging behaviours or symptoms can persist over time and in certain circumstances it may be justifiable to continue antipsychotics. Reasons for continuing antipsychotics include:[2]

- A high risk of adverse consequences if medicines are withdrawn, especially if treatment has only been partially effective or prior relapses have occurred
- When the consequences of symptom relapse are deemed to be unacceptably severe
- When no alternative treatment approaches have been possible or effective in the past

Alternatives to antipsychotics may also be considered; discussion with a Geriatrician or Psychiatrist is recommended. There is a small body of evidence to support the use of SSRIs, such as citalopram and sertraline, for agitation and psychosis in people with dementia, with no statistically significant differences found between the effectiveness of SSRIs and antipsychotics.[35] There is some limited emerging evidence that levetiracetam may be useful for the behavioural symptoms of dementia.[36]

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* HbA_{1c} should be used in preference to a fasting glucose test for investigating for diabetes in most clinical situations. However, HbA_{1c} is not reliable when blood glucose levels rise too rapidly to affect HbA_{1c} such as in some patients newly initiated on atypical antipsychotics. Therefore, in patients with other risk factors for diabetes, fasting blood glucose is recommended at baseline, and monthly for the first three months. HbA_{1c} can be used for long-term monitoring.

Further reading

The Faculty of Psychiatry of Old Age (NZ) guidelines for the use of antipsychotics in residential aged care can be downloaded from: **www.ranzcp.org/Files/ranzcp-attachments/About_Us/College_Structure/Faculties/RANZCP_Clinical_recommendations-pdf.aspx**

The Health Quality and Safety Commission's Atlas of Healthcare Variation contains data on polypharmacy in older people, including the prescription of antidepressants. For further information, see: **www.hqsc.govt.nz/our-programmes/health-quality-evaluation/projects/atlas-of-healthcare-variation/polypharmacy-in-older-people/**

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