

# Risperidone (Risperdal) for behavioural disturbances in dementia

(ris-PER-i-done)

## Summary

- Manage underlying causes of behavioural disturbances and try non-drug strategies first. Combinations of non-drug strategies tailored to the needs of individuals and carers appear to be helpful.
- Reserve drug therapy for distressing behavioural disturbances that do not respond adequately to non-drug strategies; drug treatment has uncertain benefits and may cause serious adverse effects.
- Consider safety profiles when choosing drug therapy: there is no conclusive evidence that any drug is more effective than another, but adverse-effect profiles differ.
- Start with risperidone 0.25 mg twice daily and increase the dose very slowly, monitoring closely for adverse events. The optimal dose appears to be 1 mg/day; however, dose should be individualised.
- Regularly review the need for continuing therapy. Behavioural disturbances may be short lived.
- Risperidone, like some other antipsychotics, may increase the risk of cerebrovascular events, hyperglycaemia and diabetes mellitus and causes dose-related extrapyramidal side effects, postural hypotension and somnolence.

## PBS Listing

### Authority required

Behavioural disturbances characterised by psychotic symptoms and aggression in patients with dementia where non-pharmacological methods have been unsuccessful.

This listing applies to:

- risperidone 500 microgram\* and 1 mg scored tablets
- risperidone 500 microgram and 1 mg orally disintegrating tablets (Quicklet)\*
- risperidone oral solution 1 mg per mL, 30 mL.†

### Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing on the basis of acceptable cost effectiveness compared with haloperidol. Risperidone was considered to have a lower propensity for tardive dyskinesia than haloperidol<sup>1</sup> based on a nine-month observational study in which tardive dyskinesia occurred in 32.2% of older people taking haloperidol and 5.4%

taking risperidone.<sup>2</sup> The PBAC was satisfied that the benefits of risperidone outweighed its risks in this patient group but recommended that a caution relating to the increased risk of stroke be added to the listing.<sup>3</sup> The Committee also noted that no additional clinical benefits in controlling behavioural disturbances were demonstrated at daily risperidone doses greater than 1 mg.

### Place in therapy

Drug therapy is second-line treatment for behavioural disturbances in dementia. Managing underlying causes and non-drug strategies should be tried first.

Risperidone produces modest improvements in problem behaviours characterised by psychosis and aggression; there is no conclusive evidence that it is any more effective than other drugs but it is the only atypical antipsychotic that is both TGA approved *and* PBS listed for this indication.

\* not previously PBS listed.

† new pack size — previously risperidone oral solution was only available in a 100 mL bottle.

## Manage underlying causes of the behaviour

Physical illness, delirium, pain or discomfort, depression and anxiety may all produce or exacerbate behavioural disturbances. Consider also whether the environment or interactions with others are contributing. Box 1 lists possible causes of behavioural disturbances.

Describing the behaviour in specific terms (for example, 'This person shouts "Help!" when left alone in the evenings' rather than 'agitation') may provide some clues about contributing factors.

### Box 1: Factors that may contribute to behavioural disturbances in dementia\*

Patient	Interaction	Environment
Cultural background/values/language	Poor verbal communication (speaking too fast, slurring words, mumbling)	Unfamiliar surroundings
Social history	Language too complex (confusing)	Too much noise (TV or radio left on, engine sounds, building sounds)
Impact of changes to family or work roles	Language demeaning and condescending	Competing noise
Personality traits	Not enough information and prompting given	Too much clutter and dangerous obstructions
Tiredness/sleeping problems	Poor eye contact	Visual distraction (e.g. patterned carpet)
Hungry/thirsty	Hostile or defensive tone in voice	Poor lighting (e.g. glare from reflective surfaces, confusing shadows or shapes)
Impact of feelings (frustration, sadness, anger, grief)	Hostile or defensive body language (gestures and stance)	Decor and fittings confusing
Pain/discomfort	Inappropriate or misunderstood verbal or non-verbal cues	Lack of visual prompts (e.g. not obvious where toilet is located)
Hearing problems/hearing impairment	Personal space invaded	Visual prompts that cue unwanted behaviour (e.g. coats or hats hung by the door, which cue people to go out)
Eye problems/visual impairment	Task or activity too complex	Unsafe environment
Infections/new illness	Task or activity demeaning	Uncomfortable temperature (hot/cold)
Physical movement problems	Changes to routines or activities	Lack of personal belongings
Incontinence issues	Social isolation or too much socialisation	Culturally inappropriate environment
Constipation	Minimal activity/overwhelming levels of activity	Lack of privacy and personal space
Poor dental health	Unfamiliar people/carers	Environment not sensitive to perceptual changes of dementia
Blood pressure (high or low)	Cultural and religious influences not considered	
Pre-existing illness	Preferred language not used	
Medication side effects and interactions	Feelings of person with dementia not acknowledged	
Non-compliance with or incorrect medication dose		
Progression of dementia		
Effects of dementia		

\* Adapted from *Reducing behaviours of concern: a hands on guide, Version 1*, March 2003. National Dementia Behaviour Advisory Service, Alzheimer's Australia.

### Use non-drug strategies first

Non-drug therapy is preferred: identifying and, where possible, modifying triggers for problem behaviours may help to avoid the need for drug therapy. Drug treatment has uncertain benefits and may cause serious adverse effects.

Non-drug management of behavioural disturbances in dementia encompasses a broad range of strategies (examples are available on the NPS RADAR website at <http://www.npsradar.org.au>). A discussion of the evidence for individual non-drug strategies is beyond the scope of this review. However, many studies of non-drug strategies have methodological weaknesses that limit their usefulness.<sup>4,5</sup> Although it is not possible to recommend any one strategy above another on the basis of current evidence, recent studies suggest that combinations of interventions tailored to the needs of individuals and carers can improve both patient behaviour and carer distress.<sup>6,7</sup>

The National Dementia Behaviour Advisory Service (ph 1300 639 448) provides information to health professionals and carers about dealing with problem behaviours. Aged-care assessment teams and psychogeriatric care units can also assist with developing management strategies for people with dementia.

### Consider carers' needs

A request for assistance in dealing with problem behaviours may indicate that a carer is having difficulty coping, rather than a change in patient behaviour. Ask carers about their mood and how caring is affecting them. Encourage them to seek information, support and respite, rather than waiting for them to ask for help; carers may be reluctant to mention their problems until they reach a crisis point.<sup>8</sup>

Interventions directed at carers, such as counselling, support groups, education and training, may help to reduce carer distress and improve the patient's mood.<sup>9</sup> Advice for carers about dealing with behavioural problems is available from the National Dementia Behaviour Advisory Service (ph 1300 639 448), Alzheimer's Australia and State-based Alzheimer's associations.

Be alert to indicators of changes in carers' health that may be stress related, such as weight loss or gain, sleep disturbances or increased dependence on alcohol or other drugs.<sup>10</sup>

See *Information for patients and carers* for a list of support and information services.

### Weigh up the risks and benefits of drug treatment

Reserve drug therapy for significant behavioural disturbances (such as those that are distressing or dangerous to the patient or a risk to the safety of others) that do not respond adequately to non-drug measures.

There is no conclusive evidence that any drug is more effective than another, although risperidone has the most evidence of efficacy and is currently the only atypical antipsychotic that is both TGA approved and PBS listed for the treatment of behavioural disturbances in people with dementia.

Note that adverse-effect profiles differ between drugs. Although atypical antipsychotics are less likely to cause extrapyramidal side effects than conventional antipsychotics, they may cause serious adverse effects such as cerebrovascular events and diabetes. See *Safety issues* for more information about the safety profile of risperidone and refer to the *Australian Medicines Handbook* for information about the adverse-effect profiles of various antipsychotics.

### Risperidone may improve behavioural disturbances dominated by aggression

Treatment with risperidone produces some improvement in behavioural disturbances in people with dementia whose problem behaviours are dominated by aggression.

The clinical significance of improvements in clinical trials is unclear because there is no standard measure for behavioural disturbances or agreed definition of a clinically significant response on the common behavioural rating scales.

Two published studies<sup>11,12</sup> have found statistically significant improvements in behavioural disturbances in elderly patients taking risperidone compared with placebo. Both studies had high placebo response rates and found relatively modest additional benefits with risperidone: 50% of patients taking placebo compared with 52–65% taking risperidone (depending on dose) were classified as responders\* in a pooled analysis.<sup>13</sup>

A third published study found no statistically significant difference between risperidone and placebo in the percentage of patients who responded to treatment.<sup>14</sup> A further three placebo-controlled studies are unpublished.<sup>15</sup>

\* Patients with a 30% improvement on the Behavioural Pathology in Alzheimer's disease (BEHAVE-AD) rating scale were classified as responders.

Published comparisons provide no conclusive evidence that risperidone is more effective than haloperidol<sup>14,16,17</sup> or olanzapine.<sup>18</sup>

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Alzheimer's disease study is comparing the effectiveness of olanzapine, quetiapine, risperidone and placebo in people with Alzheimer's disease and behavioural disturbances. Results are expected to be available in 2006.

## Safety issues

Elderly patients are more susceptible than younger patients to the adverse effects of risperidone.

Adverse effects such as extrapyramidal side effects (EPS), postural hypotension and somnolence are dose related<sup>12</sup>, underlining the need for low doses and careful dose titration (see *Dosing issues*). Consider each patient's risk of cerebrovascular adverse events and diabetes mellitus; risperidone may increase the risk of both.

Risperidone has a lower propensity for anticholinergic adverse effects (such as dry mouth, constipation and delirium) than most other antipsychotics.<sup>19</sup>

For a comprehensive list of possible adverse effects, see the Risperdal Product Information.

Report adverse events to ADRAC online (see <http://www.tgasime.health.gov.au>) or by using the 'Blue Card' distributed with the *Schedule of Pharmaceutical Benefits*. For information about adverse event reporting, see the TGA website (<http://www.tga.gov.au>).

### Consider the risk of cerebrovascular events

Risperidone appears to increase the risk of cerebrovascular adverse events in elderly people with dementia<sup>20</sup>, especially in the presence of other risk factors for cerebrovascular disease. There is some evidence of a similar risk with olanzapine.<sup>21</sup> The elevated risk seen in clinical trials has been in comparison with placebo; a recent large observational study found a similar rate of ischaemic stroke in elderly people with dementia taking either atypical or conventional antipsychotics.<sup>22</sup>

Ask patients and/or carers to report any signs of possible cerebrovascular events promptly, such as sudden weakness or numbness in the face, arms or legs, and speech or vision problems.

The potential risk of cerebrovascular adverse events with risperidone was raised by an Australian trial in which cerebrovascular adverse events (mainly strokes and transient ischaemic attacks) occurred in 1.8% of people in the placebo group and in 9% in the risperidone group.<sup>11</sup> All patients who experienced cerebrovascular adverse events had significant risk factors, such as hypertension, atrial fibrillation and diabetes mellitus.<sup>11</sup>

In six placebo-controlled trials in mainly elderly people with dementia, cerebrovascular adverse events occurred in 33/989 (3.3%) of patients treated with risperidone and 8/693 (1.2%) of patients treated with placebo.<sup>13</sup>

### Hyperglycaemia and diabetes mellitus

Risperidone, olanzapine, quetiapine and clozapine have been associated with a higher risk of new-onset diabetes and hyperglycaemia than conventional antipsychotics.<sup>23</sup> There is most evidence for an increased risk with clozapine or olanzapine.<sup>23</sup> Whether this risk applies equally to younger patients with schizophrenia and elderly patients with dementia is unknown.

Given that elderly people are likely to be at higher cardiovascular risk than younger patients, careful consideration should be given to the possibility of elevating their risk further.

It has been suggested that<sup>23</sup>:

- people with diabetes who start risperidone be monitored for worsening diabetic control
- people considered to be at high risk of diabetes have fasting blood glucose tests at the beginning of treatment and periodically during treatment
- patients treated with risperidone be monitored for symptoms of hyperglycaemia, such as polydipsia, polyuria, polyphagia and weakness.

## Extrapyramidal side effects are dose related

Use the lowest possible dose of risperidone because the risk of EPS, such as tremor, rigidity, bradykinesia, akathisia and acute dystonia, is dose related.<sup>12,13</sup> Daily doses from 1 mg may increase the risk of EPS relative to placebo in elderly people with dementia (Table 1).<sup>12</sup>

As with all antipsychotics, risperidone should be used with extreme caution in people with Parkinson's disease or Lewy-body dementia (which accounts for up to 20% of dementia cases in the elderly and is characterised by visual hallucinations, parkinsonism, fluctuating alertness, and falls), who are particularly susceptible to extrapyramidal side effects.<sup>13</sup> Note that anticholinergic drugs used to treat EPS can exacerbate confusion and may precipitate delirium.

There is little information about the comparative incidence of EPS with risperidone and other antipsychotics in elderly people with dementia. Three studies have reported less severe EPS with risperidone (mean daily dose 0.8–1.1 mg) than with haloperidol (mean daily dose 0.83–1.2 mg)<sup>14,16,17</sup>, but only one reported the relative frequency of EPS (15% with risperidone vs 22% with haloperidol).<sup>14</sup>

## Monitor for tardive dyskinesia

Elderly people are at particular risk of irreversible tardive dyskinesia. Limit the dose and duration of treatment with risperidone to minimise the risk of tardive dyskinesia. Ask patients and carers to report any abnormal movements of the face, arms, legs and trunk promptly. If movements suggestive of tardive dyskinesia occur, consider ceasing risperidone.

Clinical trials of risperidone in elderly people with dementia have been limited to 12 weeks or less, which is not long enough to assess the risk of tardive dyskinesia, which develops with chronic use of antipsychotics. One 9-month observational study of middle-aged and older people with psychotic symptoms or behavioural disorders indicates that risperidone is less likely than haloperidol to cause tardive dyskinesia.<sup>2</sup>

## Dosing issues

Starting doses and target doses should be lower and dose titration slower in the elderly than in younger patients. Consider ceasing or reducing the dose if adverse effects such as postural hypotension and EPS occur.

The prescribing information for risperidone recommends a starting dose of 0.25 mg twice daily, increasing by 0.25 mg/day every two or more days.<sup>13</sup> A risperidone dose of 0.25 mg is equivalent to half a 500 microgram tablet or 0.25 mL of oral solution. Note that risperidone orally disintegrating tablets should not be halved.

The optimal dose appears to be 1 mg/day; higher doses have no additional clinical benefit and an increased risk of adverse events.<sup>12</sup> However, dosage should be individualised. Some patients may benefit from daily doses of up to 2 mg.<sup>13</sup> Once the target dose has been achieved, once-daily dosing can be considered.<sup>13</sup>

Regularly review the need for continuing therapy with a view to reducing or ceasing the dose. Behavioural disturbances may be short lived, so drug therapy should not be prescribed indefinitely. Minimising drug exposure is important to limit the risk of adverse effects.

## Information for patients and carers

Ask patients and/or carers to report signs of possible adverse effects promptly, such as:

- abnormal movements of the face, trunk and limbs
- dizziness or fainting on standing
- sudden weakness or numbness in the face, arms or legs, or speech or vision problems
- worsening of diabetic control, or the occurrence of possible indicators of diabetes (such as persistent excessive thirst or hunger or passing more urine than normal).

**Table 1: Dose-related incidence of extrapyramidal side effects (EPS) associated with risperidone in a 12-week trial in people with dementia<sup>12</sup>**

	Daily risperidone dose			
	Placebo	0.5 mg	1 mg	2 mg
<b>Patients with EPS (%)</b>	7.4%	6.7%	12.8%	21.2%

Suggest or provide the Risperdal Consumer Medicine Information (CMI) leaflet.

Encourage carers and people with dementia to seek support and provide them with information about available services (Box 2).

The National Dementia Behaviour Advisory Service (ph 1300 639 448) can provide advice to carers about dealing with behaviours of concern in people with dementia. Help sheets about understanding and managing problem behaviours in dementia are available from the Alzheimer's Australia website (<http://www.alzheimers.org.au>).

### Box 2: Information and support services for carers and people with dementia

#### Alzheimer's Australia (see <http://www.alzheimers.org.au>) and State-based Alzheimer's associations

- Co-ordinate support groups, information sessions and free specialist counselling services for carers and patients, provide help sheets on aspects of caring for people with dementia, provides the National Dementia Helpline (Ph 1800 639 331).

#### Dementia Behaviour Management Advisory Service (Ph 1300 699 799)

- Advice about managing behaviours of concern for those who care for a person with dementia. Available 24 hours a day to respite care staff, health professionals and carers.

#### Commonwealth Carer Resource Centres (Ph 1800 242 636)

- Provide information about services and support for carers and coordinate the National Carer Counselling Program, which provides short-term counselling to reduce carer stress, improve carer coping skills and facilitate continuation of the caring role.

#### Commonwealth Carelink Centres (Ph 1800 052 222)

- Assist with information and access to services (such as household help, assistance with meals and social groups) to support older people and people with disabilities living independently in the community.

#### Commonwealth Carer Respite Centres (Ph 1800 059 059)

- Co-ordinate a wide variety of respite services, including in-home, day care and residential respite care.

#### Aged and Community Care Information Line (Ph 1800 500 853)

- Provides information about Community Aged Care Packages, residential care fees in Australian Government-funded facilities and Aged Care Assessment Teams.

#### Carers associations (see Carers Australia website at <http://www.carersaustralia.com.au> for details of State-based associations)

- Facilitate access to local and national support services and education.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.