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Risperidone use in people with dementia: what do the new restrictions mean?

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Objectives

- Describe the theory underpinning medication management of changed behaviour associated with dementia (BPSD)
- Evaluate the appropriateness of risperidone use for BPSD
- Explain approved and off- label prescribing

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Contents

- Review of the pathophysiology of dementia
- Role of medications in managing dementia
- Antipsychotics and changed behaviour
- Approved indications and off-label prescribing

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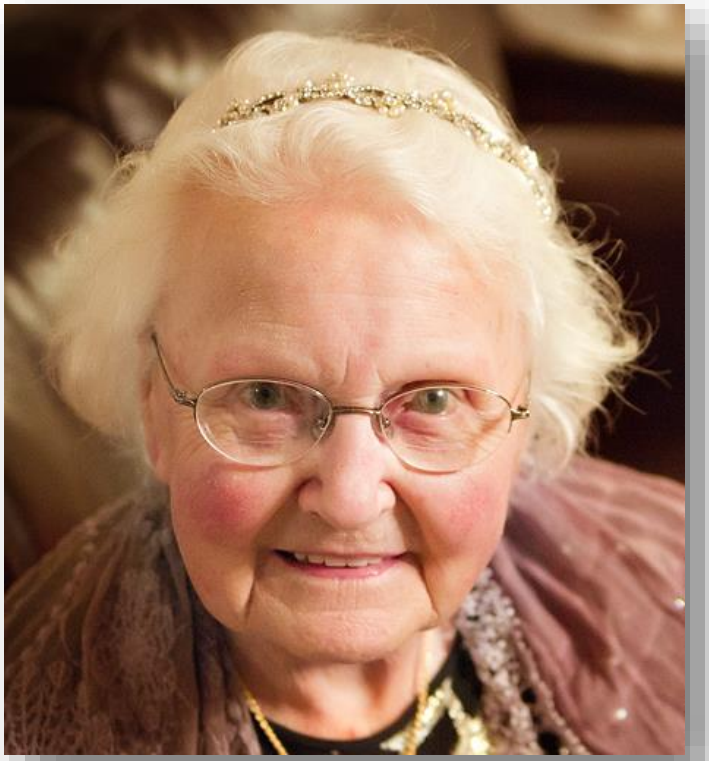
Meet Betsy

- 92 y.o.
- New resident at aged care home
- Admitted from home where son was primary carer
- Son no longer able to cope due to her disturbed sleep patterns and poor memory



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Betsy – medical history

- Alzheimer's disease
- Osteoporosis with vertebral stress fractures
- Deafness (bilateral hearing aids)
- Limited mobility (high falls risk)
- GORD
- Hypotension
- Nocturia

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Betsy - medications

Morning

- Aspirin 100mg
- Iron 325mg
- Calcium and Vitamin D 600mg/ 25μg
- Fish oil 1000mg
- Esomeprazole 20mg
- Fludrocortisone 0.1mg
- Multivitamin

Evening

- Risperidone 0.5mg
- Probiotic
- Cranberry 10 000mg
- Solifenacin 5mg

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- Osteoporosis (vertebral ##)
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- Limited mobility (high falls risk)
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What is the role of risperidone in Betsy's medication management?

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Dementia

*A **syndrome** characterised by an **irreversible** loss of mental ability severe enough to **interfere with normal activities of daily living**, **lasting more than six months**, **not present since birth**, and **not associated with a loss or alteration of consciousness***

- Most common types AD, vascular dementia, Lewy body dementia and frontotemporal dementias
- Also occurs in PD, Huntington's disease, progressive supranuclear palsy, CJD and other prion disorders, and neurosyphilis
- Patients can have > 1 type (mixed dementia)

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The role of medications in the management of dementia

Role	Agents used
Cure disease	Nothing even on the horizon
Prevent disease or delay onset	Nothing promising
Slow progression of disease	Studies disappointing to date
Treat primary symptoms e.g. memory	Anticholinesterases * NDMA antagonists *
Treat secondary symptoms e.g. depression, hallucinations	Antipsychotics Sedatives
*only registered for use in Alzheimer's disease	

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Medications for behavioural and psychological symptoms of dementia

- Psychological and behavioural symptoms integral manifestations of dementia
  - Behavioural symptoms: e.g. physical aggression, screaming, restlessness, agitation, wandering, culturally inappropriate behaviours, sexual disinhibition, hoarding, cursing and shadowing.
  - Psychological symptoms: e.g. anxiety, depressive mood, hallucinations and delusions
- Non-pharmacological approaches first line for BPSD because of a favourable balance of benefits and harms
- Drug therapy should not be first-line for patients with BPSD

Antipsychotics

- Antipsychotic actions are thought to be mediated (at least in part) by blockade of dopaminergic transmission in various parts of the brain. Evidence suggests:
  - all effective antipsychotics block D_2 receptors
  - differential blockade of other dopamine receptors (e.g. D_1) may influence therapeutic and adverse effects
  - antagonism of other receptors may influence antipsychotic activity, e.g. $5HT_2$ antagonism with some agents

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Antipsychotics (continued)

- Includes typical (e.g. haloperidol) and atypical (risperidone, olanzapine and quetiapine) agents
- Reserve for residents with distressing agitation, aggression, delusions or psychoses
- Ineffective in treating wandering or disinhibition
- Benefits generally small
  - RCTs indicate modest positive outcomes in 18-26% of residents
- Risk of AEs are high
  - Increased risk of mortality, stroke and extrapyramidal symptoms

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If pharmacotherapy is considered necessary

Hallucinations, delusions or seriously disturbed behaviour:

- Risperidone 0.25 mg twice daily, increasing by 0.25 mg every 2 or more days if necessary (max. 2 mg/day)

OR

- Olanzapine 2.5 mg daily, increasing by 2.5 mg every 2 or more days (max. 10 mg daily)

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Adverse effects of antipsychotics

AEs frequent as antipsychotics affect multiple neurotransmitter receptor types and subtypes

- Common: sedation, anxiety, agitation, EPSE, orthostatic hypotension, tachycardia
- Olanzapine and some older agents: blurred vision, mydriasis, constipation, nausea, dry mouth, urinary retention
- Avoid typical antipsychotics in residents with Lewy bodies dementia or Parkinson's disease

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Extrapyramidal side effects

- Incidence dose-related
  - Highest with haloperidol, lowest with some of the newer agents
- Reduce antipsychotic dose to avoid recurrent EPSE when possible
- Avoid anticholinergic drugs (e.g. benztropine)
  - May add to anticholinergic effects and worsen tardive dyskinesia and cognition

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Some extrapyramidal side effects may be mistaken for BPSD

- Dystonias
  - Torticollis, carpopedal spasm, trismus, perioral spasm, oculogyric crisis, laryngeal spasm and opisthotonos
- Akathisia
  - Feeling of motor restlessness; usually occurs 2–3 days (up to several weeks) after starting treatment
  - May present as agitation secondary to psychosis
- Parkinsonism
  - Tremor, rigidity or bradykinesia; usually develops after weeks or months
- Tardive dyskinesia
  - Involuntary movements of the face, mouth or tongue, and sometimes head and neck, trunk or limbs

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Mortality risk

- Clozapine, olanzapine and quetiapine, associated with increased blood glucose, weight gain and dyslipidaemia
  - Clozapine and olanzapine associated with increased risk of type 2 diabetes
- Increased death rate noted in placebo-controlled trials of aripiprazole, olanzapine, quetiapine and risperidone in dementia patients
  - Mostly due to cardiovascular events or infections
  - One death associated with antipsychotic use for every 100 patients treated over **10–12 weeks**
- Olanzapine and risperidone associated with increased risk of fatal and non-fatal strokes and TIAs
  - Other antipsychotics may carry similar risks of death or stroke

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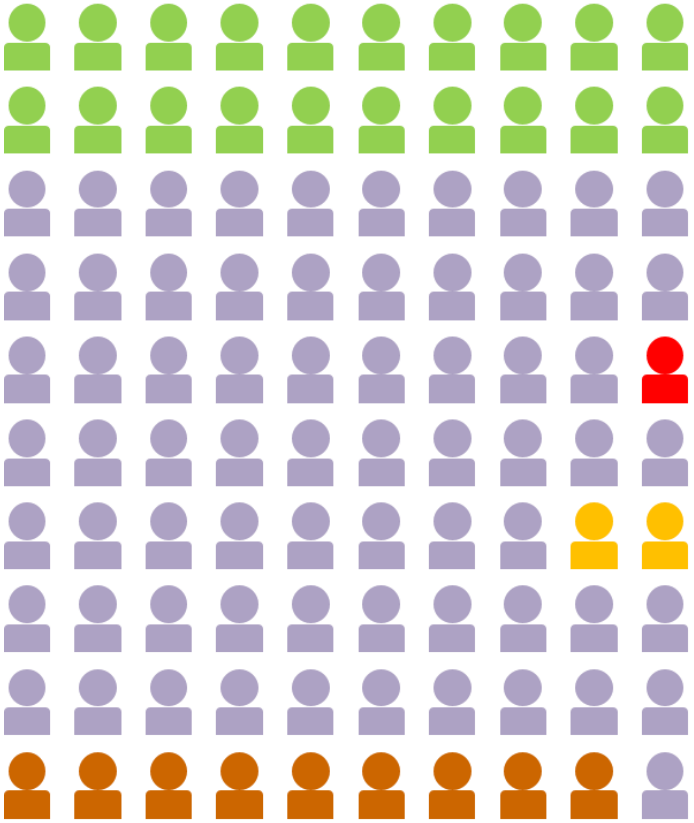
Short-term risks and benefits

If 1000 people were treated with an antipsychotic for **12 weeks:**



91-200

PEOPLE SHOW CLINICALLY SIGNIFICANT IMPROVEMENTS

10 ADDITIONAL **DEATHS**

18 ADDITIONAL **CEREBROVASCULAR EVENTS**

58-94

PEOPLE WITH **DISTURBED GAIT**

DOI: 10.1002/14651858.CD003476.pub2

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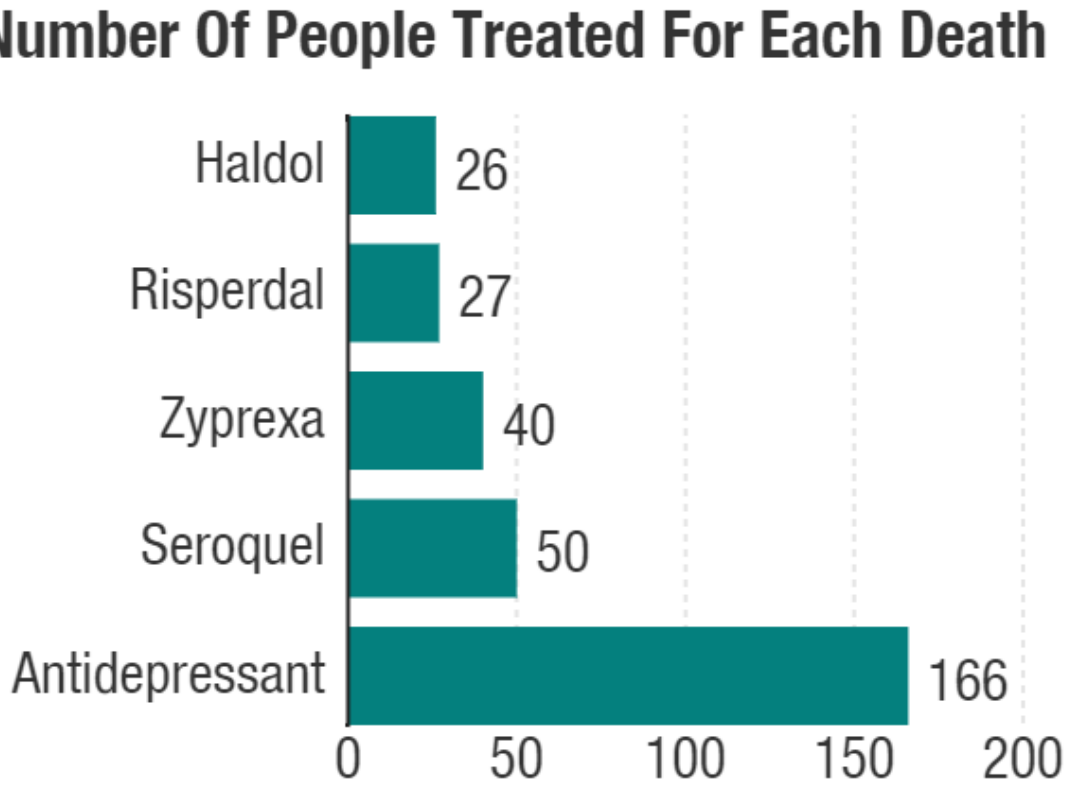
Longer term risks and benefits

Treating people with dementia with psychotropics for **6 months:**



JAMA Psychiatry. 2015;72(5):438-44

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Risperidone and dementia types

- Risk of CVA increased for patients being treated with risperidone for vascular or mixed dementia, compared with those taking it for Alzheimer's dementia
  - Odds ratio for vascular or mixed dementia 5.26 (95% CI 1.18 to 48.11)
  - Comparative odds ratio for Alzheimer's dementia 2.23 (95% CI 0.85 to 6.88)

DOI: 10.1002/14651858.CD003476.pub2

TGA restricts dementia drug risperidone following stroke link

JOEL MAGAREY | THE AUSTRALIAN | AUGUST 12, 2015 12:00AM

SAVE

The federal drugs regulator has restricted official approval of a popular antipsychotic used to treat tens of thousands of Australians with dementia because of "troubling" findings linking the drug to dramatically increased rates of stroke.

The Therapeutic Goods Administration said it had received data indicating a more than fivefold higher risk of "cerebrovascular adverse events" — stroke or transient ischaemic attack — in patients with vascular or mixed dementia on risperidone. One expert, University of Sydney professor of geriatric medicine David Le Couteur, said this meant about 1500 to 2000 more strokes a year in that patient population.

Drug company Janssen-Cilag, which developed risperidone, has revealed the adverse events data it supplied to the TGA were based on a re-analysis of the results of trials conducted more than a decade ago.

The TGA's tightened regulation has been welcomed by advocates and experts concerned antipsychotics are being used to make managing elderly people with dementia easier despite significant risks some drugs pose to such patients.

Older people with dementia are particularly susceptible to the side-effects of antipsychotics, which are often described as the "cornerstone" of treatment for psychotic illnesses such as schizophrenia.

Professor Le Couteur said the increased risk of stroke was "troubling" and the restriction "very much a change in the right direction". "However, it is very worrying that changes in the registered indication are occurring only now, 10 to 15 years after the safety data were available."

It is believed the risperidone restrictions will apply to most of the estimated 70,000 Australians with dementia who are prescribed antipsychotics.

OPINION 3 OF 4

MAURICE NEWMAN

The Bureau of Meteorology needs to open its records to closer public scrutiny.

IN NATIONAL AFFAIRS

QNI gave Palmer Party $5.95m

JARED OWENS

Queensland Nickel, now under voluntary administration, was the single largest donor to the PUP last financial year.

Crossbench to view secret union report

Employment Minister Michaelia Cash is refusing to show the contentious sixth volume to Labor and the Greens.

'I'll persuade voters over GST'

DAVID CROWE

Scott Morrison says he can convince Australians of the need for an unpopular increase in the

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Risperidone changes - August 2015

- Prior to August 2015, risperidone was approved in Australia for the treatment of behavioural disturbances in all types of dementia
- Approval now limited to treatment (up to 12 weeks) of moderate to severe dementia only of the Alzheimer type
- Other indications remain unchanged:
  - treatment of schizophrenia and related psychoses
  - short-term treatment of acute mania associated with bipolar 1 disorder
  - treatment of conduct and other disruptive behaviour disorders in children (>5y.o.), adolescents and adults with sub-average intellectual functioning or mental retardation in whom destructive behaviours are prominent
  - treatment of behavioural disorders associated with autism in children and adolescents

DOI: 10.1002/14651858.CD003476.pub2

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Off-label prescribing

When a drug is prescribed for an indication, a route of administration, or a patient group that is not included in the drug's approved product information

- Therapeutic Goods Administration (TGA) responsible for approving indications, route/s of administration and patient group
- "Off label" does not mean that the TGA has rejected the indication
  - Commonly the TGA has not been asked to evaluate the indication
- Off-label prescribing is not illegal and may sometimes be appropriate

Aust Prescr 2013;36:182-3

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Risperidone PBS listing

- Behavioural disturbances
  - Clinical criteria:
    - The condition must be characterised by psychotic symptoms and aggression, AND
    - Patient must have dementia, AND
    - Patient must have failed to respond to non-pharmacological methods of treatment

http://www.pbs.gov.au/medicine/item/1842y Cited 15 February 2016

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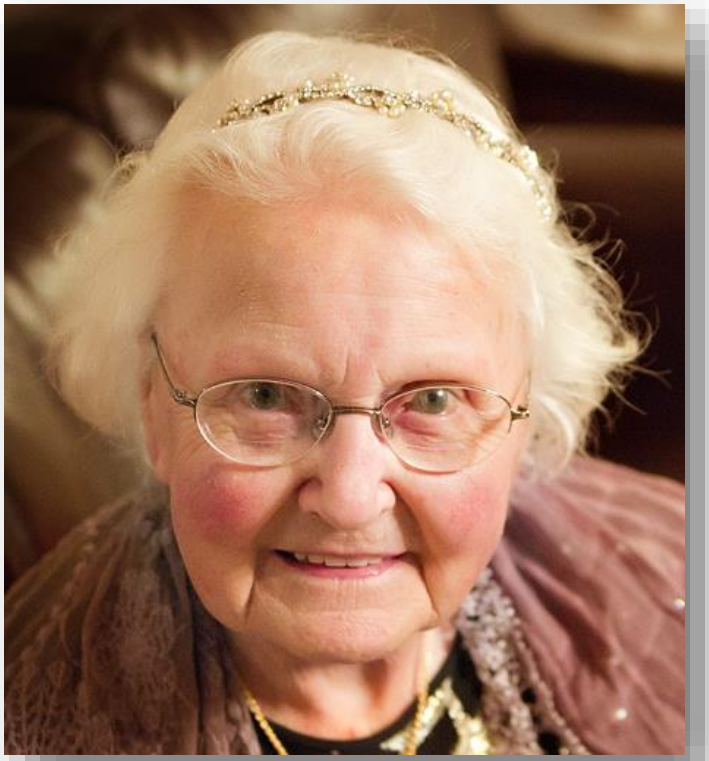
Using a medication off-label

- There is no legal impediment to prescribing off label
  - onus on the prescriber to defend their prescription for an unlisted indication
- If the prescriber believes that the off-label prescription can be supported by reasonable quality evidence, proceed if this is in the patient's best interests
- It is best if the patient/ guardian knows the prescription is off label and why the drug is being used
- Note this in the patient's records, possibly even record consent
  - This approach is not different from what should ideally be done for the prescription of any drug
  - The rationale for off-label prescription might be subject to more scrutiny in the case of a serious adverse event

Aust Prescr 2013;36:182-3

What does all this mean for Betsy?



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Betsy's use of risperidone

- Commenced by her former GP several months ago when she was still living at home
  - Wandering aimlessly about the house throughout the night
  - Wanting to use the toilet incessantly
- Staff reported that she is very settled in her new surroundings
  - Wanders at night but responds well to redirection
- No current issues with, or history of, agitation, aggression or psychotic symptoms

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Does Betsy need risperidone?

Benefit **Risk**

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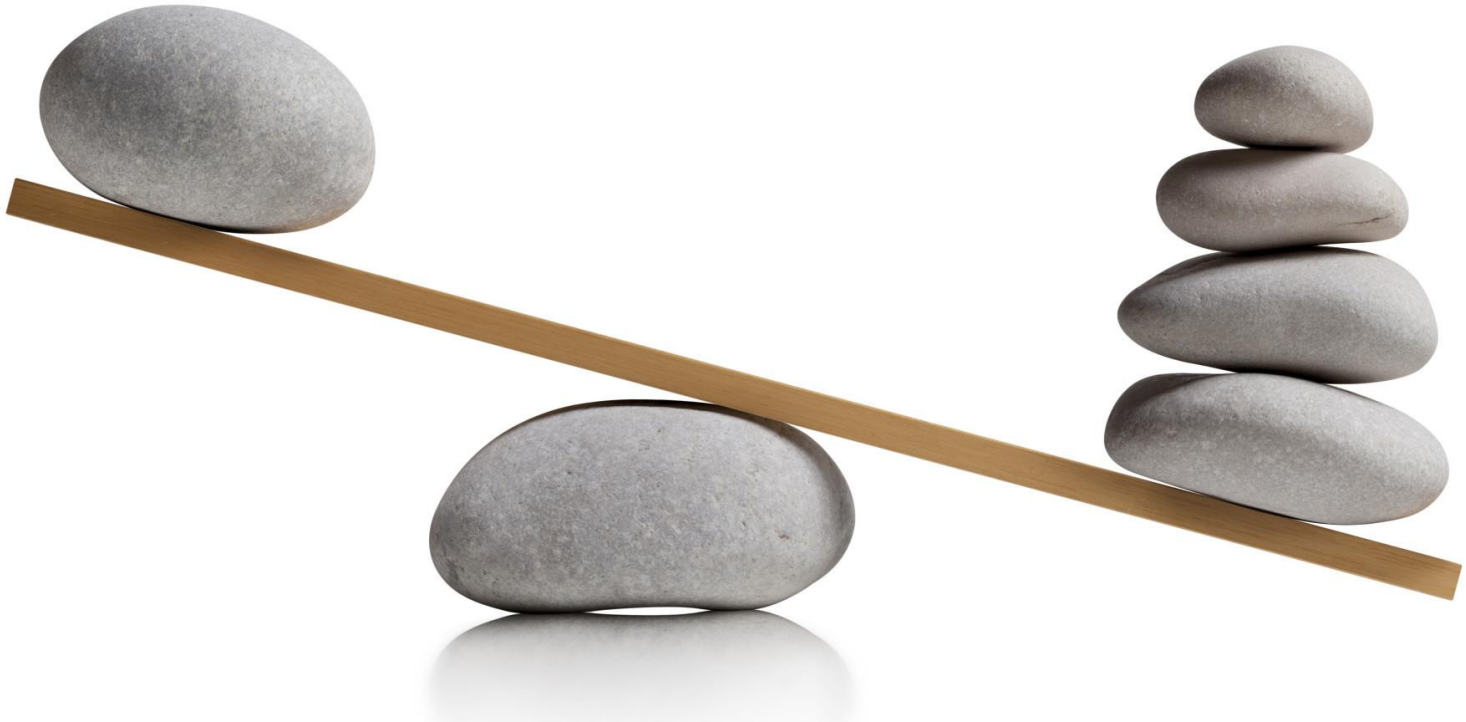
Does Betsy need risperidone?

Benefit **Risk**



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Withdrawal of antipsychotics

2013 systematic review

- Evaluated whether withdrawal of antipsychotic agents is successful in older people with dementia in community or RACF
- 9 trials included, 606 participants
  - Both abrupt and gradual withdrawal strategies used
  - Different drugs at different doses in all trials
- Overall: No difference between group whose antipsychotic was withdrawn and those continuing, but follow-ups short (3 months)
- Subgroups: Those with worse NPS at baseline were more likely to relapse

Cochrane Database Syst Rev. 2013 Mar 28;3:CD007726

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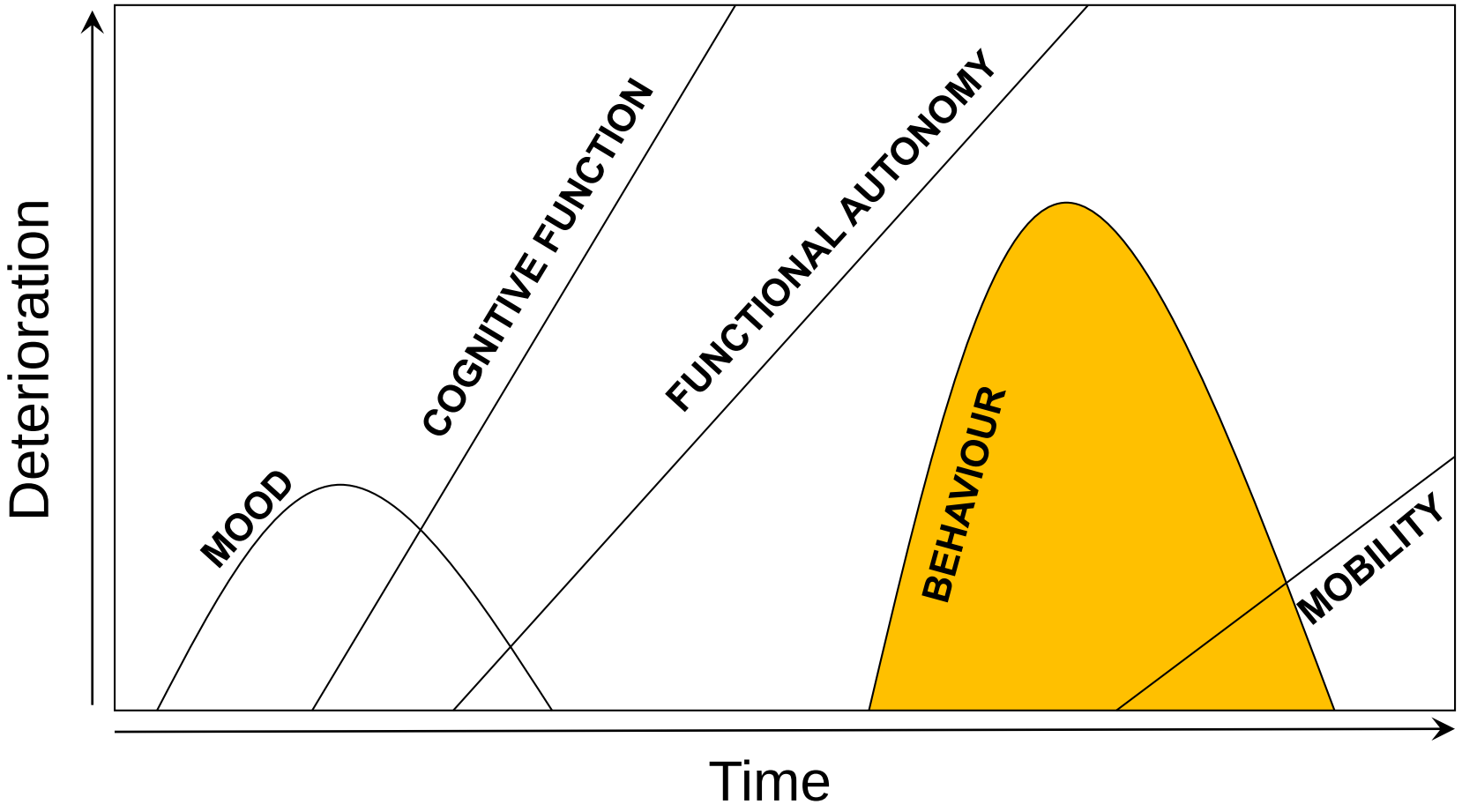
Alzheimer's progression



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Conclusions

- Whilst antipsychotics are frequently used in the management of BPSD, their effectiveness is limited in most people
- All antipsychotics are associated with a risk of serious adverse effects when used for BPSD
- Risperidone's approved indication for use has been limited to people with Alzheimer's dementia, for no more than 12 weeks
- Whilst it is best practice to avoid the use of risperidone for BPSD associated with other dementia types, it is not illegal to do so