Mental Health Prescribing
for
People over 65years old
in
Tasmania

Best Practice Principles
for Prescribing
Anxiolytics, Antidepressants and Antipsychotics
for Older People

Experts in Medicines
CPS CONSULTANT PHARMACY SERVICES

Contents

Introduction and Background

Older people make up an increasing proportion of the Tasmanian population with the growth in the number of people 65 or over being more than twice as fast as the overall population growth. In the 2011 Census, almost 1 in 6 Tasmanian's were aged 65 or more, an increase of 9% over the previous 5 years and 17% over the previous 10 years (see Table 1).[1]

Age Group	Census Date					
	2001		2006		2011	
	#	%	#	%	#	%
65-69 years	16,901	3.70%	19,556	4.15%	23,780	4.86%
70-74 years	15,691	3.44%	15,737	3.34%	18,335	3.75%
75-79 years	13,170	2.88%	13,686	2.91%	13,868	2.84%
80-84 years	8,506	1.86%	10,536	2.24%	10,848	2.22%
85 years and over	7,010	1.54%	8,437	1.79%	10,103	2.07%
Total Tasmanian Population	**456,652**	**13.42%**	**470,797**	**14.43%**	**489,026**	**15.73%**

Table 1: Proportion of Tasmanian Population over 65 years of Age (Adapted from 1)

With ageing comes a higher prevalence of multiple medical conditions and an increase in mental health concerns. Approximately 10-15% of older Australian have depression and anxiety (higher, approximately 35%, in residential aged care) and less common psychiatric conditions, such as schizophrenia, occur almost twice as frequently as in younger people (2.3% compared to 1.3%).[2] Older people are at greater risk of minor problems having more of a psychological impact and any psychological illness may be compounded by other comorbidities.

Multiple medications are often used to manage the varied co-morbidities in older people. Older people are, however, at a greater risk of adverse reactions from the medications that they take due to altered handling of the medication and often altered sensitivity to the effects of the medication. The medications used in mental health disorders are, by definition, active in the central nervous system, and these agents in particular may cause significant adverse effects in older people.

The aim of this document is to review the prescription use of anxiolytics, antidepressants and antipsychotic agents in Tasmania and develop information relating to their appropriate use to assist health professionals caring for older patients with mental health disorders. Because of the increasing prevalence of dementia as a comorbidity for patients with anxiety, depression and sleep disorders, a section of the efficacy of the agents of interest in people with dementia will be included.

Prescribing Rates in Tasmania

Information in this section is modified from the Australian Atlas of Heathcare Variation, and is based on Pharmaceutical Benefits Scheme (PBS) prescription data from 2013/14 and the Australian Bureau of Statistic population data for 30th June 2013.[3]

PBS prescriptions represent the majority of medications dispensed in Australia, and the price to the consumer is subsidised by the Australian Government. However, a significant number of medications are now being dispensed as non-PBS prescriptions at prices below the subsidised price for the consumer. As such the PBS statistics in the section below may under-represent the number of prescriptions dispensed in Tasmania.

In the 2014 version of the Australian Statistics on Medicines, the proportion of non-PBS prescriptions for the agents of interest varied, with PBS prescription numbers under-representing actual dispensings by 7 to 54% (see Table 2).[4]

Drug Group	PBS Prescriptions	Non-PBS Prescriptions	Non-PBS/PBS Prescriptions
Anxiolytics	4960624	1436558	28.96%
Antidepressants	14719811	7878190	53.52%
Antipsychotics	3650876	241226	6.61%

Table 2: PBS and Non-PBS prescriptions for Mental Health Medications in 2014 (from 4)

Anxiolytics

Almost 90% of all the anxiolytics in Australia are one of diazepam, temazepam or oxazepam (see Table 3). It is assumed that the Tasmanian pattern of prescribing is similar as state specific data is not available for anxiolytic prescribing.

Anxiolytic Name	PBS Prescriptions in 2014	Non-PBS Prescriptions in 2014	Total	
			#	%
DIAZEPAM	1,785,384	644,235	2,429,619	38.0
TEMAZEPAM	1,659,444	546,415	2,205,859	34.5
OXAZEPAM	923,676	140,302	1,063,978	16.6
NITRAZEPAM	328,636	38,572	367,208	5.7
ALPRAZOLAM	237,695	67,025	304,720	4.8
ZOPICLONE	22,262	9	22,271	0.3
FLUNITRAZEPAM	2,526	0	2,526	0.0
BROMAZEPAM	829	0	829	0.0
MIDAZOLAM	153	0	153	0.0
BUSPIRONE	37	0	37	0.0
Total	**4,960,642**	**1,436,558**	**6,397,200**	**100.0**

Table 3: Number of Prescriptions Dispensed for Anxiolytics in Australia in 2014 (Adapted from 4)

The prevalence of use of anxiolytic agents in older people in Australia is difficult to quantify. One study of almost 4000 older primary care patients found that 19.6% of women over 65 years old and 10.8% of men received prescriptions for benzodiazepines over the 12 months of 2002.[5] Of the 625

people who received at least one prescription, 40% received only one, 45% between two and six and 15% seven or more.[5] A study of the use of benzodiazepines in nursing homes in Tasmania found an overall prevalence of approximately 30% in 2009 and 25% in 2011.[6,7]

The per capita PBS prescribing rates for patients over 65 years old are shown in Figure 1.

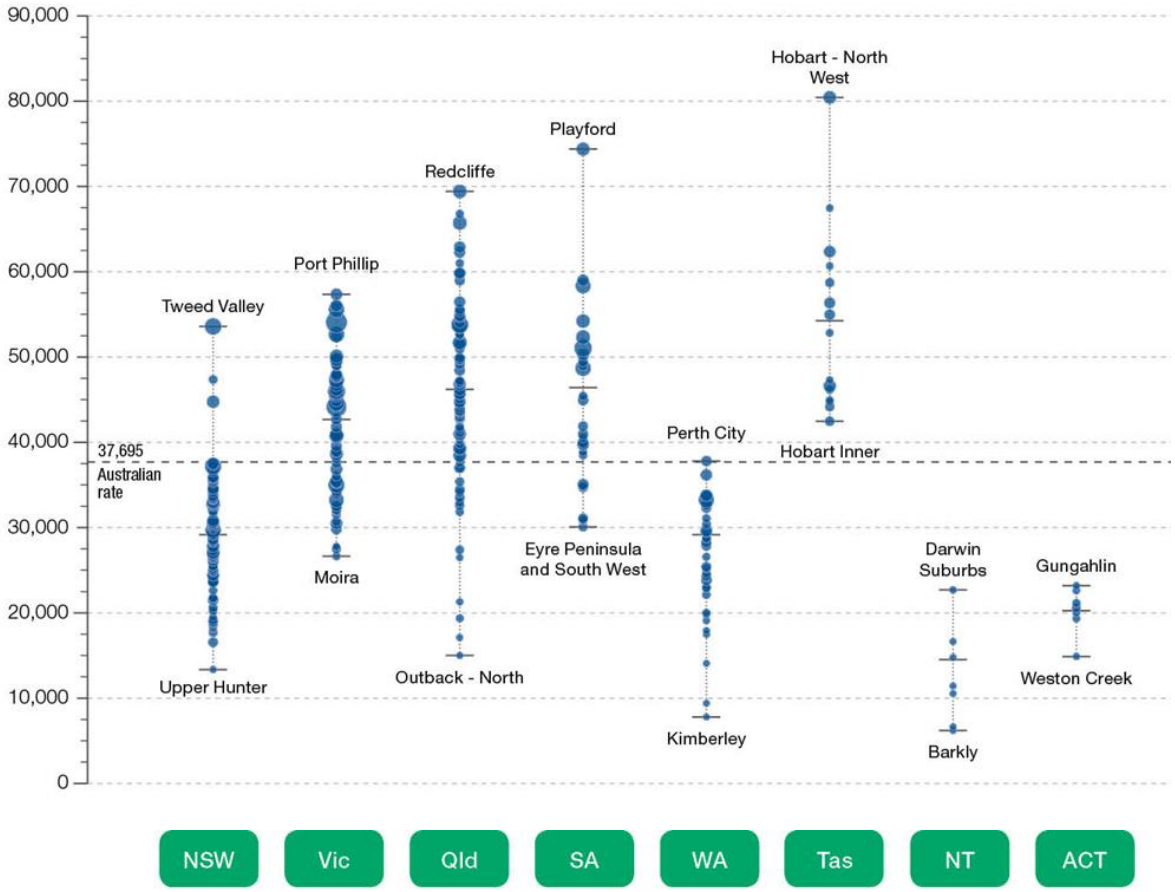


Figure 1: Per Capita PBS Prescription Rates for Benzodiazepines in Australia (from 3)

As can be seen, the single highest prescribing rate in Australia is in the north-west region of Hobart in Tasmania, where the rate of prescribing is over twice that of the Australian average. All other regions of Tasmania are above the National average, with seven regions in the top 10% of the Nation (see Table 4).

Anxiolytics					
SA3 name	**Estimated Resident Population over 65yo June 2013**	**PBS Prescriptions (2013/14)**	**Prescription rate per 100,000 (Australian Average 37695)**	**Percentile**	**Ranking (of 325 SA3 Regions)**
Hobart - North West	8939	7258	81195	99.96	1
Brighton	1797	1149	63940	99.13	4
Burnie - Ulverstone	9396	5888	62665	97.61	8
Central Highlands	1803	975	54077	96.78	11
Hobart - South and West	5023	2948	58690	95.54	16
Hobart - North East	9173	5167	56328	93.45	20
Devonport	8612	4682	54366	91.92	25
Sorell - Dodges Ferry	2394	1291	53926	89.25	36
South East Coast	1849	805	43537	79.1	66
Launceston	13739	6598	48024	77.34	73
Meander Valley - West Tamar	4448	1944	43705	76.42	75
Huon - Bruny Island	3472	1429	41158	73.24	87
West Coast	2782	1172	42128	72.57	92
North East	7490	3238	43231	71.57	97
Hobart Inner	7669	3456	45065	66.64	111
	88586	**48000**	**54185**		

Table 4: Tasmanian Regional Data for Prescriptions for Anxiolytics (adapted From 3)

Antidepressants

Australia has a high use of antidepressants overall, with almost 24 million prescriptions for antidepressants dispensed in 2014 (see Table 5).

Drug name	PBS Prescriptions in 2014	Non-PBS Prescriptions in 2014	Total	
			#	%
SERTRALINE	1822397	1635038	3457435	15.3
ESCITALOPRAM	1575792	1659163	3234955	14.3
VENLAFAXINE	1799494	994006	2793500	12.4
AMITRIPTYLINE	1426767	591542	2018309	8.9
MIRTAZAPINE	1492446	450441	1942887	8.6
DESVENLAFAXINE	1902545	3243	1905788	8.4
CITALOPRAM	1019046	718811	1737857	7.7
FLUOXETINE	796885	745389	1542274	6.8
DULOXETINE	1129253	191213	1320466	5.8
PAROXETINE	600010	432906	1032916	4.6
DOTHIEPIN	305725	126604	432329	1.9
FLUVOXAMINE	253025	168610	421635	1.9
DOXEPIN	205141	47157	252298	1.1
NORTRIPTYLINE	97200	41017	138217	0.6
MOCLOBEMIDE	82563	38166	120729	0.5
CLOMIPRAMINE	55221	19246	74467	0.3
REBOXETINE	50846	420	51266	0.2
MIANSERIN	41135	7185	48320	0.2
IMIPRAMINE	23643	7512	31155	0.1
TRANYLCYPROMINE	17703	519	18222	0.1
BUPROPION	15779	1	15780	0.1
PHENELZINE	7195	1	7196	0.0
Total	**14719811**	**7878190**	**22598001**	**100.0**

Table 5: Number of Prescriptions Dispensed for Antidepressants in Australia in 2014 (Adapted from 4)

The most commonly dispensed agents were sertraline, escitalopram and venlafaxine (making up over 1/3 of all use).

Dispensing of antidepressants per capita in patients over 65 years of age does not seem to be greatly different to the Australian averages (see Figure 2).

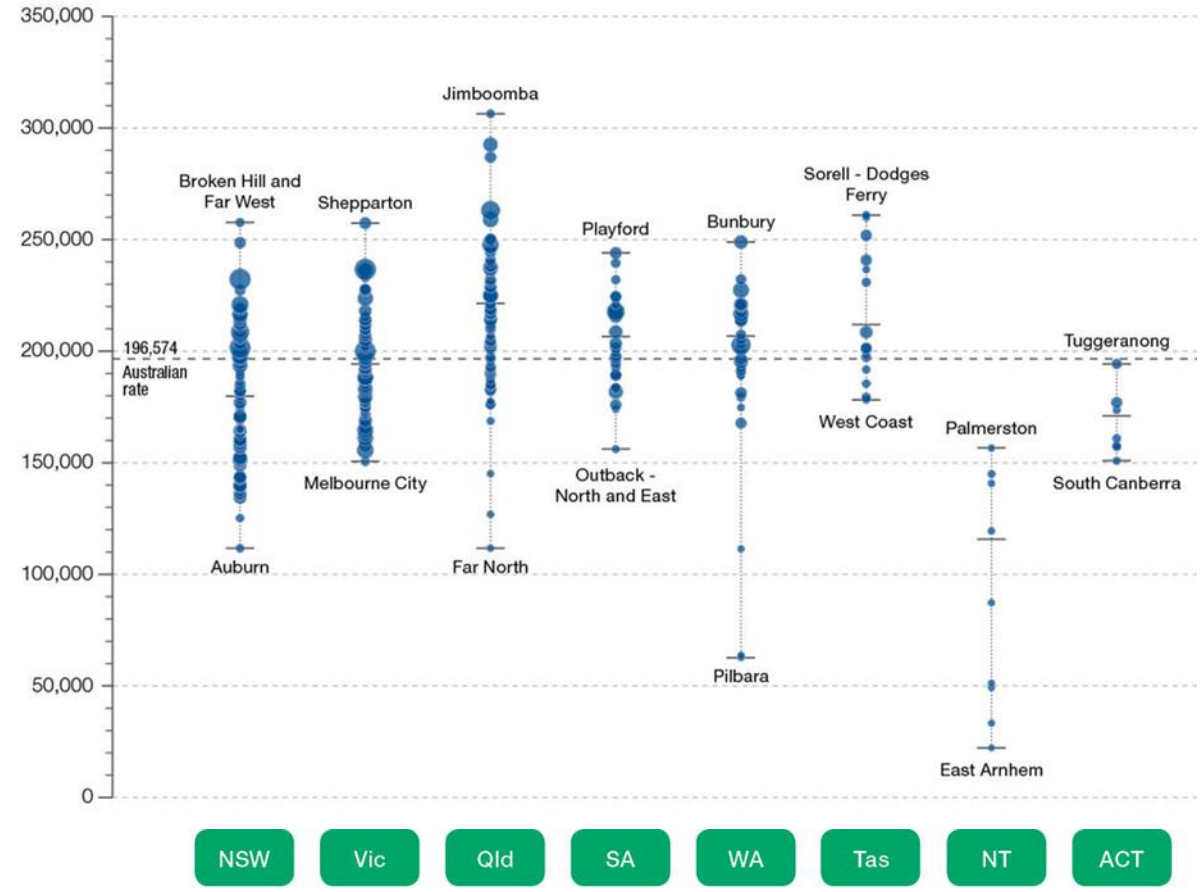


Figure 2: Per Capita PBS Prescription Rates for Antidepressants in Australia by State (from 3)

Four of the regions in Tasmania are in the top 10% of dispensing rated for antidepressants in the over 65 ear old age group (see Table 6).

Antidepressants					
SA3 name	**Estimated Resident Population over 65yo June 2013**	**PBS Prescriptions (2013/14)**	**Prescription rate per 100,000 (Australian Average 196574)**	**Percentile**	**Ranking (of 325 SA3 regions)**
Sorell - Dodges Ferry	2394	6286	262573	96.5	5
Central Highlands	1803	4420	245147	96.4	6
Hobart - North West	8939	22595	252769	94.3	10
Hobart - North East	9173	22115	241088	90.1	22
Brighton	1797	4325	240679	88.0	31
Hobart - South and West	5023	11597	230878	84.7	45
Launceston	13739	28826	209811	66.6	109
Burnie - Ulverstone	9396	19031	202544	59.5	137
Devonport	8612	17415	202218	58.8	141
South East Coast	1849	3480	188210	56.0	152
Hobart Inner	7669	15477	201812	55.3	157
Huon - Bruny Island	3472	6588	189747	49.3	184
Meander Valley - West Tamar	4448	8204	184442	42.6	207
North East	7490	13323	177877	36.3	231
West Coast	2782	4878	175341	35.3	232
	88586	**188560**	**212855**		

Table 6: Tasmanian Regional Data for Prescriptions for Antidepressants (adapted From 3)

Antipsychotics

Antipsychotic use in Australia is largely under the supervision of specialist psychiatrist. As can be seen from the list of agents dispensed in this category (Table 7), the most commonly dispensed agents are olanzapine, quetiapine and risperidone (accounting for 2/3 of all dispensed antipsychotic prescriptions). The PBS guidelines for use for many of these agents require initiation in consultation with, or by a specialist psychiatrist for specific mental health conditions.

Drug Name	PBS Prescriptions in 2014	Non-PBS Prescriptions in 2014	Total	
			#	%
OLANZAPINE	990,677	37,662	1,028,339	26.2
QUETIAPINE	934,339	54,131	988,470	25.2
RISPERIDONE	616452	34092	650544	16.6
CLOZAPINE	292,005	19,837	311,842	7.9
ARIPIPRAZOLE	175657	35	175692	4.5
PALIPERIDONE	162094	49	162143	4.1
LITHIUM	102,710	57,746	160,456	4.1
HALOPERIDOL	79,231	9610	88,841	2.3
AMISULPRIDE	84,118	3,229	87,347	2.2
CHLORPROMAZINE	61,261	10,674	71,935	1.8
PERICYAZINE	40,388	9,916	50,304	1.3
ZIPRASIDONE	38,667	9	38,676	1.0
ZUCLOPENTHIXOL	30,116	1,420	31,536	0.8
ASENAPINE	29,752	9	29,761	0.8
TRIFLUOPERAZINE	22,633	3,512	26,145	0.7
FLUPENTHIXOL	13,147	422	13,569	0.3
FLUPHENAZINE	7,745	293	8,038	0.2
Total	**3,680,992**	**242,646**	**3,923,638**	**100.0**

Table 7: Number of Prescriptions Dispensed for Antipsychotics in Australia in 2014 (Adapted from 4)

It is not clear from the Australian information available, what proportion of antipsychotic use is for patients 65 years of age or over. The per capita PBS prescribing rates for the different states in Australia are shown in Figure 3.

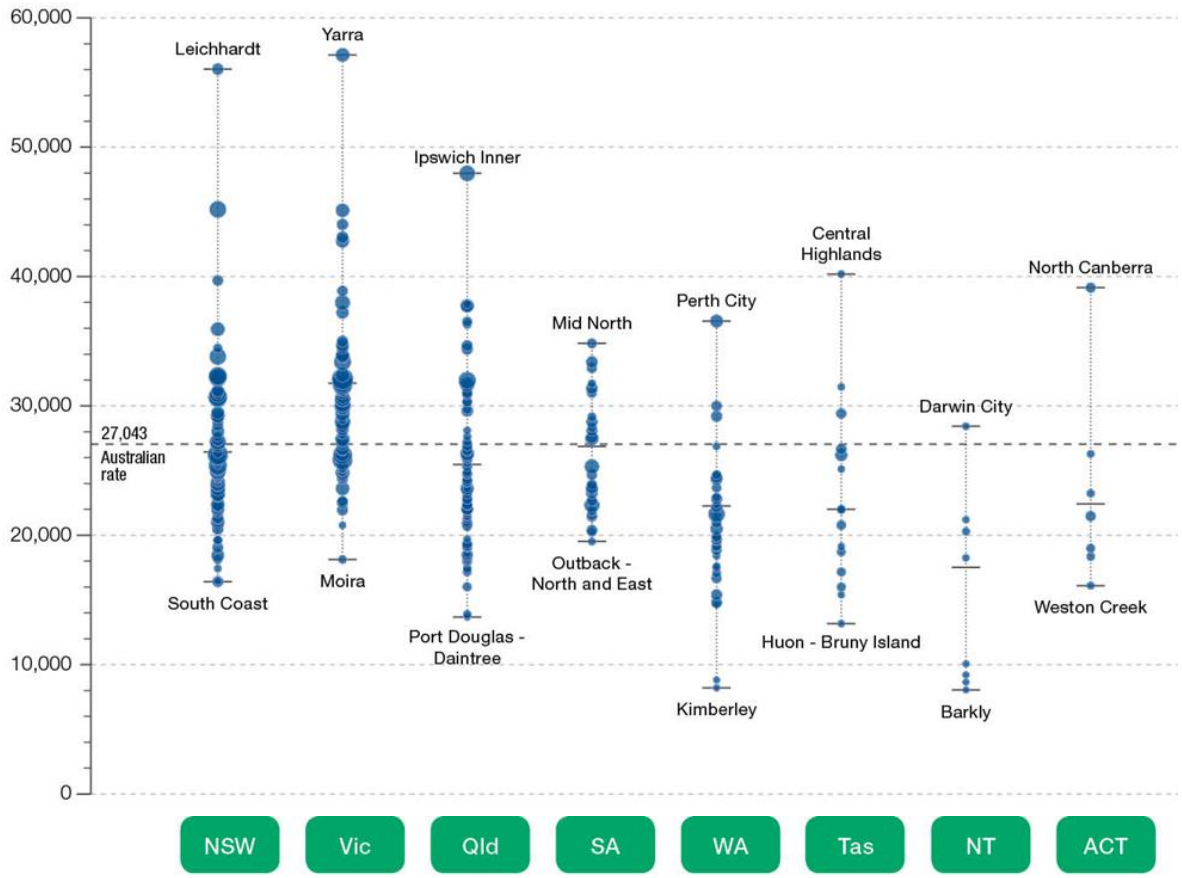


Figure 3: Per Capita PBS Prescriptions for Antipsychotic in Australia (from 3)

It can be seen that the Tasmanian rates of prescribing are not dissimilar to those in other States, and as is shown in Table 8, the average per capita prescription frequency for over 65 year olds in Tasmania is lower than the National average.

Antipsychotics					
SA3 name	**Estimated Resident Population over 65yo June 2013**	**PBS Prescriptions (2013/14)**	**Prescription rate per 100,000 (Australian Average 27043)**	**Percentile**	**Ranking (of 325 SA3 Regions)**
Central Highlands	1803	629	34886	98.5	9
South East Coast	1849	487	26339	81.3	51
Hobart Inner	7669	2414	31477	72.2	79
Hobart - North West	8939	2453	27442	57.6	116
Launceston	13739	3720	27076	54.8	128
Brighton	1797	396	22037	48.6	152
Meander Valley - West Tamar	4448	919	20661	31.2	222
Hobart - South and West	5023	1114	22178	31.1	223
Burnie - Ulverstone	9396	1951	20764	25.2	253
Sorell - Dodges Ferry	2394	441	18421	18.1	276
North East	7490	1280	17089	16.6	284
Devonport	8612	1502	17441	11.6	303
Hobart - North East	9173	1477	16102	8.6	311
West Coast	2782	396	14234	7.3	312
Huon - Bruny Island	3472	383	11031	3.8	318
	88586	**19562**	**22082**		

Table 8: Tasmanian Regional Data for Prescriptions for Antipsychotics (adapted From 3)

Older Patients and Mental Health

Mental Health Conditions

Functional and clinical symptoms of mental illness are complex in old age, often driven by previous mental health issues, medical co-morbidity, social and inter-personal issues and are often confounded by acute illness, cognitive impairment, and a range of complex presentations. Patients may be averse to describing or initiating discussions of mental health due to poor recognition, social stigma or time limitations and may instead present a focal symptom (ie: come to GP stating 'unhappy with care' , 'chronic pain', 'poor sleep') requesting a medication solution.

Best practice is to formulate a comprehensive care plan with patient centred focus and engagement in the specific modalities utilised. In mild cases these should be focussed on non-pharmacological strategies, primarily counselling and community supports. There is increasing evidence for enhanced community engagement and exercise programmes in older people, which address multiple factors (social isolation, pain, frailty, nutrition, mental heath) providing better comprehensive care. Examples are; senior citizen's services, local council programmes (eating with friends, bus outings, community gardens),U3A (shared learning and diversity), exercise (physiotherapy, exercise physiologist, strength to strength) socialisation and peer based re-enforcement.

In moderate to severe cases the model is usually multi-modal and referral can be made to specialist older persons' mental health services for case management and service co-ordination.

There may be the additional challenges of limited support networks, poor access to allied health (transport, availability), and cost is often a barrier.

Secondary issues of poor engagement with non-pharmacological modalities, time utilisation, who is responsible, realistic overall aims, counselling for expected outcomes.

The following sections focus on the more common and clinically relevant mental health conditions in older people.

Anxiety

Anxiety is often manifested as an escalation of health concerns, social isolation, phobias, insomnia or chronic pain.

Often these symptoms have been prevalent throughout life but the person has previously adapted to managed these. In the older person, pre-existing anxiety symptoms can be exacerbated by illness, delirium, loss of social supports, cognitive impairment, dis-inhibition and inability to engage in reassurance and CBT techniques.

Depression

There are a vast range of presenting symptoms for depression in older patients. Depression has an increasing prevalence in old age and is especially common is association certain medical co-morbidities.[8] These include:

- Cardiac disease (20-30%)
- CVA (20% -esp left hemisphere, or frontal with lability)
- Cancer (25% -higher for pancreatic and oro-pharangeal malignancies 50%)
- Diabetes (up to 27% depending on complications)
- Hypothyroid, fibromyalgia, Arthritis and chronic pain
- Prodromal dementia and mild vascular cognitive impairment

Adjustment disorder is common in older patients and may be related to personal symptoms and signs or related to the persons role as a carer.

Common issues that directly impact on the older person's likelihood of developing adjustment disorder are:

- loss of function, role, and independence
- chronic pain
- grief (spousal or other)
- accommodation changes (especially moving into residential care -45% rate)
- life losses, previous trauma, Post Traumatic Stress Disorder

Some situations where the older person's role as a carer results in fatigue and stress (and a likely adjustment disorder as a consequence) are

- a high spousal care burden
- caring for children with dis-abilities
- family expectations (ie: grandchildren and financial needs)

Cognitive impairment, Dementia and Delirium

There is an increasing prevalence of cognitive impairment and dementia with age. The rates of dementia increase with age to 65-80% by age 85yo. There are a number of prodromal psychiatric symptoms such as anxiety and depression that are increasingly recognised for dementia. It is still, however, difficult to predict if progression to dementia will clearly follow these. The best evidence of progression to Alzheimer's dementia is in patients with amnestic mild cognitive impairment.

Recognition of vascular cognitive impairment is poor, but it is highly prevalent in a range of disease co-morbidity, most especially in: CVA, TIA, post cardiac surgery, diabetes. But there is great difficulty in predicting progression and symptom profile for an individual.

Frontal and global impairments in those with alcohol and substance use disorders, with some scope for improvement of cognition and overall health with abstinence. But limited success in old age, and also limited access to age appropriate services and facilities for residential support if requested.

Mental Health Medications and Older People

Older patients undergo changes in body characteristics as a result of both ageing and various morbidity accumulation. As a result, older patients often have a reduced reserve in one or more body systems. Insults to these systems (infections, drugs and exacerbations of underlying conditions) have a greater impact on patients with limited reserve.

With regard to response to medications, older patients often have both altered pharmacokinetics (their body's ability to absorb, metabolise and eliminate the drug) as well as altered pharmacodynamics (their body's sensitivity to the same amount of circulating medication).

Pharmacokinetic changes in Older People

With aging, there are changes in the absorption, distribution, metabolism and elimination of medications with some changes are more clinically relevant. The metabolism and excretion of many drugs decrease, requiring that doses of some drugs be adjusted. Toxicity may develop slowly because levels of chronically used drugs increase over time, until a steady state is achieved. For example, log acting benzodiazepines such as diazepam, have half-lives of several days in older people and signs of toxicity may not appear until days or weeks after therapy is started.

Absorption

Despite an age-related decrease in small-bowel surface area, slowed gastric emptying, and an increase in gastric pH, changes in drug absorption tend to be clinically inconsequential for most mental health drugs of interest.

Distribution

With age, body fat generally increases and total body water decreases. Increased fat increases the volume of distribution for highly lipophilic drugs (eg, diazepam, tricyclic antidepressants) and may increase their elimination half-lives.

Hepatic metabolism

Overall hepatic metabolism of many drugs through the cytochrome P-450 enzyme system decreases with age. Hepatic clearance of drugs metabolized by phase I reactions is more likely to be prolonged in older people (eg diazepam). Usually, age does not greatly affect clearance of drugs that are metabolized by conjugation (phase II reactions- eg oxazepam). First-pass metabolism (metabolism, typically hepatic, that occurs before a drug reaches systemic circulation) is also affected by aging, decreasing by about 1%/yr after age 40.

In addition, many of the enzymes responsible for metabolism of the mental health drugs of interest are polymorphic, with significant interindividual variation in metabolism as a result of genetics (see Table 9).

Genotype	2D6	2C9	2C19
Poor Metabolisers	10%*	4%*	3-21%
Intermediate Metabolisers	35%	38%	24-36%
Extensive Metabolisers	48%	58%	79-97%
Ultra Extensive Metabolisers	7%*		

Table 9: Prevalence of Different Genotypes for Selected CYP 450 Isoenzymes (from 9).

Further, there are additional medications and environmental factors (eg smoking cigarettes) that can induce or inhibit the various enzymes. Some of the mental health drugs themselves are involved as

factors in altering the metabolism of other agents (see Table 10). For example paroxetine is a potent CYP2D6 inhibitor and can interact significantly with a number of agents (eg tamoxifen).[10,11]

As a result there is often a wide variation in the nature of drug metabolism in older patients. As some metabolites are active, or have particular toxic effects, this means that some patients may have altered response and increased risk of adverse effects to some medications.

Taken together, the genotype and phenotype information relating to particular drugs (and their metabolites) may enable the prediction of both response to and adverse effects from mental health and other medications.[12,13,14,15]

Renal elimination

One of the most important pharmacokinetic changes associated with aging is decreased renal elimination of drugs. After age 30, creatinine clearance decreases an average of 8-10 mL/min/1.73 m2/decade. Serum creatinine levels often remain within normal limits despite a decrease in GFR because older people generally have less muscle mass and are generally less physically active than younger adults and thus produce less creatinine. The use of serum creatinine alone as an estimate of renal elimination of drugs can overestimate the capacity of older people to eliminate medication. The recent introduction of the estimated glomerular filtration rate (eGFR) to most pathology reports potentially exacerbates this situation, as bodyweight is not included as a factor in the formula that is involved in calculating the eGFR.

The clinical impact on drugs depends on the extent that renal elimination contributes to total systemic elimination and on the drug's therapeutic index. Creatinine clearance (measured or estimated using computer programs or a formula, such as Cockcroft-Gault) is used to guide drug dosing. The daily dose of drugs that rely heavily on renal elimination should be lower and/or the frequency of dosing should be decreased. Because renal function is dynamic, maintenance doses of drugs may need adjustment when patients become ill or dehydrated or have recently recovered from dehydration.

Drug	Active Metabolites (half life) and Relative Activity (percent activity)	CYP450 Enzymes Involved	Impact on Drug Metabolism Enzymes
Anxiolytic Agents			
DIAZEPAM	Desmethyldiazepam (40-120) -active (100%) Temazepam (8-15) low levels- inactive Oxazepam (5-15) low levels- inactive	2C19, 3A4	
TEMAZEPAM	none		
OXAZEPAM	none		
NITRAZEPAM	none		
ALPRAZOLAM	4-hydroxyalprazolam- less active (50%)	3A group	
Antidepressant Agents			
SERTRALINE	N-desmethylsertraline (62 - 104)- less active (12%)		Inhibitor of 2D6
ESCITALOPRAM	S-demethylcitalopram- less active (20%)	2C19, 3A4, 2D6	Inhibitor of 2D6
VENLAFAXINE	*O*-desmethylvenlafaxine -active (100%)	2D6	weak inhibitor of CYP2D6
AMITRIPTYLINE	Nortriptyline (18-44) - active (100%)	2D6, 2C19	
MIRTAZAPINE	N-desmethylmirtazapine -active	3A4 1A4, 2D6	weak inhibitor of 1A2, 2D6, 3A4
DESVENLAFAXINE	none		weak inhibitor of 2D6
CITALOPRAM	demethylcitalopram - less active didemethylcitalopram - less active citalopram-N-oxide- less active	2C19, 2D6	weak inhibitor of 1A2, 2D6, 2C19
FLUOXETINE	norfluoxetine (96-384)- active (100%)	2D6	Inhibitor of 2D6
DULOXETINE	None	2D6, 1A2	Inhibitor of 2D6
PAROXETINE	85% first pass metabolism	2D6	Inhibitor of 2D6
DOTHIEPIN	desmethyldothiepin- active (100%)		
FLUVOXAMINE	deoxyfluvoxamine -less active	1A2, 2D6, 2C19	Inhibitor of 1A2, 2C9, 2C19
Antipsychotic Agents			
OLANZAPINE	4'-N-desmethylolanzapine- less active 2-hydroxy-methylolanzapine- less active	1A2, 2D6, 2C19	
QUETIAPINE	norquetiapine (12)- active	3A4 2D6, 2C9	
RISPERIDONE	9-hydroxy-risperidone (24)- active (100%) 7-hydroxy-risperidone - less active	2D6	
HALOPERIDOL	hydroxyhaloperidol- less active	3A4, 2D6	Inhibitor of 2D6

Table 10: Hepatic Metabolism of Mental Health Drugs of Interest (from 10,16,17)

Drug Induced Mental Health Issues

As part of the management of any medical issue, modification of any causative factors (where possible) is a standard approach. There are a number of medications that may contribute to or directly cause a range of mental health issues. Before initiating treatment with benzodiazepines, antidepressant or antipsychotics in older people, a review of the potential for a reversible medication-related contributor to the symptoms would be appropriate.

Drug Induced Insomnia

There are multiple mechanisms by which medications can interfere with sleep. Some have a direct action on sleep parameters such as time to get to sleep (sleep latency) and total time asleep, while others may impact more if there is a withdrawal state (eg benzodiazepines) or if they cause physical changes that cause waking during the night (eg diuretics causing nocturia). A summary of some of the direct effects of medications known to cause or contribute to insomnia is shown in Table 11. Note that benzodiazepines have been included to assist in understanding the changes that occur with long term use (after tolerance has developed) and with cessation after long term use. In addition, three common substances that are used in society (alcohol, caffeine and nicotine) are included, as often modifying the use of these substances can improve insomnia significantly.

Medication	Impact on sleep parameters				
	REM%	Sleep Continuity	Sleep Latency	Slow Wave Sleep %	Total Sleep Time
Alcohol	Less		Shorter		
Amphetamines	Less		Longer		Less
Anticonvulsants					
Antipsychotics	Less		Shorter		More
Benzodiazepines <4 weeks	Less	More	Shorter	Less	More
Benzodiazepines >6 weeks	Less		None	Less	None
Benzodiazepine withdrawal	More				
Beta agonists					
Beta Blockers	More	Less			
Caffeine		Less	Longer		Less
Clonidine	Less			More	More
Levodopa					
Lithium	Less			More	
Methyldopa				More	
Nicotine	Less	Less	Longer		Less
NSAIDs	Less	Less			
Opioids	Less	Less			Less
SSRIs/SNRIs	Less	Less	Longer		
Steroids	Less			Less	
Thyroxine					
Tricyclic antidepressants	Less		Shorter		More

Table 11: Impact of Medications on Sleep Parameters (from 18,19,20 ,21, 22, 23)

As can be seen, the majority of agents impact by reducing the proportion of REM sleep. This is often perceived by the patient as poor quality sleep and can be reported as insomnia on presentation. For example, antipsychotics increase the total amount of sleep and reduce the time taken to get to sleep, but reduce REM sleep.

Drug Induced Anxiety

A number of the stimulant medications that interfere with sleep do so as a result of their direct stimulatory effects on brain activity. These stimulatory effects may also increase feelings of anxiety. Medications that can contribute to anxiety are:

- Amphetamines
- Beta agonists
- Corticosteroids
- Levodopa
- Methyldopa
- Oral Contraceptives
- Phenytoin
- Pseudoephedrine
- Theophylline
- Thyroxine

Drug Induced Depression

There are number of drugs and drug groups that have been implicated as contributors to or causes of depression. Although the evidence for a clear causative association for many of the agents is weak, clinicians would be prudent to (where appropriate and feasible) consider alternative agents to the suspected causes prior to initiating an antidepressant agent. A list of purported agents and some relevant comments is shown in Table 12.

Drug or Drug Group	Comments on Evidence
ACE Inhibitors	Initial reports were observational, not confirmed in randomised trials.
Acyclovir	
Angiotensin II receptor blockers	Some case reports with valsartan and losartan.
Anticonvulsants	
Benzodiazepines	Possible cause based on GABAergic effects
Beta blockers	Related to central activity and lipophilicity. Most common with propranolol and carvedilol.
Calcium Channel Blockers	Case reports for nifedipine, diltiazem and verapamil. Not substantiated by randomised studies.
Corticosteroids	Commonly cause depression and other psychiatric symptoms (mania, hypomania, paranoia, psychosis). Dose related.
Diuretics	Initial reports not substantiated. Probably related to electrolyte abnormalities
Dopamine agonists	
Finasteride	Depression can develop within a few months of commencement
Fluoroquinolones	
Interferon	Induce depression in ~30% of users
Isotretinoin	Known cause
Levonorgestrol	Common reason for cessation. Depression develops in first 3 months of use
Methyldopa	Known cause
Montelukast	Known cause of depression and other psychiatric symptoms (hallucinations)
Opioids	
Statins	
Varenicycline	High risk of depression, anxiety and abnormal dreams during initiation of therapy

Table 12: Medications Potentially Contributing to Depression (From 88)

Anticholinergic Burden and Mental Health Disorders

Anticholinergic drugs act on the muscarinic system and inhibit acetylcholine-mediated responses. They are used in a range of conditions such as Parkinson's disease and in the management of urinary incontinence.

Anticholinergic agents have a range of side effects that are peripheral (constipation, dry mouth, bloating and anorexia) and ophthalmic (dry eyes, blurred vision, diplopia). They also, however, have a wide range of central nervous system adverse effects that can mimic some mental health disorders (see Figure 4).

Anticholinergics have been shown to be associated with an increased risk of hospitalisation for confusion or dementia. Admission for this reason within one year occurred in 1.2% of the control group and in 1.4% of patients taking one drug with anticholinergic properties, 3% of those taking two drugs, and 4.3% of those taking three or more drugs with anticholinergic properties.(NNH 500, 55 and 24 respectively). [24] Anticholinergic burden is also associated with an increased incidence of delirium, a longer hospital stay and a higher level of dependence at discharge.[25] There has also been a link made between anticholinergic medication use and mortality.[26]

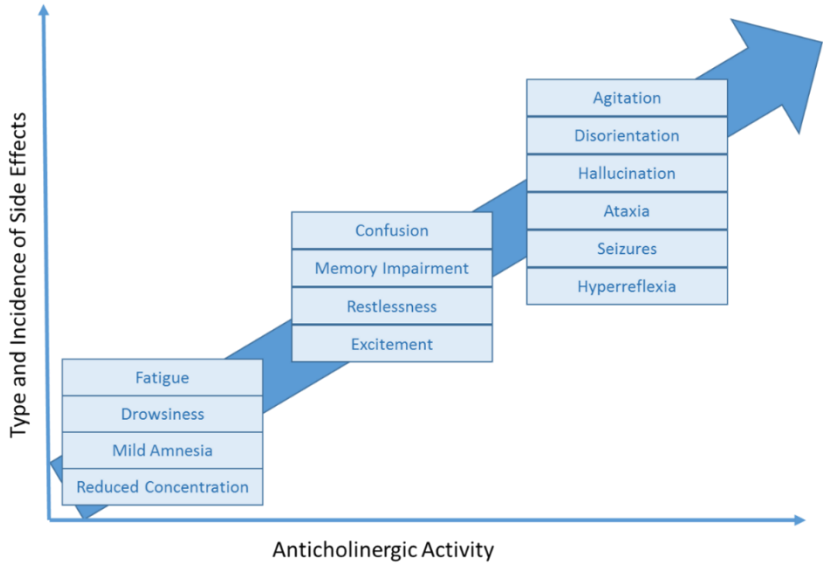


Figure 4: Central Side Effects with Increasing Anticholinergic Activity (adapted from 27)

In addition to these major effects, more subtle impact on cognition, brain metabolism and brain atrophy have been reported in cognitively normal older patients.[28]

While pure anticholinergic agents such as benztropine and oxybutynin have clear effects, there are many agents that are not primarily intended as anticholinergics that have varying degrees of pharmacological anticholinergic properties. These include agents such as corticosteroids, H_2 receptor antagonists, digoxin and diuretics (see Table 13).

Common Medications with Anticholinergic Properties	
Analgesics	Codeine NSAIDs Tramadol
Antihistamines	Promethazine, clemastine
Cardiovascular	Angiotensin Converting Enzyme inhibitors Beta Blockers Calcium Channel Blockers Class I antiarrhythmics Digoxin Frusemide Nitrates
Gastrointestinal	Hyoscine Loperamide Ranitidine, cimetidine
Miscellaneous	Antibiotics Corticosteroids
Neurological	Alprazolam, oxazepam Antipsychotic agents Benztropine Paroxetine Tricyclic antidepressants
Respiratory	Ipratropium, tiotropium Theophylline

Table 13: Selected Medications with Anticholinergic Properties (from 27, 29)

A drug burden index has been developed that incorporated the anticholinergic load and the sedative potential of medications.[30] This allows clinicians to estimate the relative impact of each of the components of the person's medication regimen on drug burden.

Best Practice Principles for Prescribing of Mental Health Medications for Older People

Anxiolytics

The anxiolytic class of agents consists of benzodiazepines and similar agents and their predominant use is for anxiety and insomnia. Some agents are specifically used as anticonvulsants, for preoperative preparation and in palliative care situations. This section will focus on the use of these agents for insomnia, for relief of anxiety symptoms and for anxiety disorders. Long term use is of particular concern as a result of the occurrence of benzodiazepine dependence.

As shown in the section regarding prescription rates, there are more prescriptions (per capita) for benzodiazepines for over 65 year old people in Tasmania than in other areas of Australia. All 15 regions in Tasmania are in the top 33% of dispensing rates, with seven of the regions being in the top 10%.[3]

Clinical Pharmacology of Benzodiazepines

Anxiolytics are also sometimes referred to as minor tranquillisers and their overall pharmacological effect is to produce inhibitory effects throughout the brain.

Gamma Amino Butyric Acid (GABA) is thought to be the major inhibitory neurotransmitter in the central nervous system and benzodiazepines are one of several drug classes that enhance its action. The GABA receptor has multiple subtypes and there are more specific receptor subtypes for sleep, anxiety and amnesia. [31]Although these subtypes of receptors exist, there is little difference between the relative affinities of the currently available benzodiazepines in terms of their pharmacological effects. As such, most benzodiazepines may be used therapeutically for their anxiolytic, anticonvulsant, hypnotic, amnesic and muscle relaxant effects (see Table 14).

Area of Brain Affected by Benzodiazepine	Clinical Effect
Cerebral Cortex	Drowsiness Cognitive impairment
Mesolimbic Dopamine System	Reduced fear and anxiety Dampening of emotions
Hippocampus	Memory impairment Anticonvulsant effects
Cerebellum and Motor Areas	Impairment of balance Reduced motor control Reduced muscle tone Reduced coordination

Table 14: Clinical Effects of Benzodiazepines.

There are significant differences between the various benzodiazepines and related agents in terms of their duration of action, with many of the agents having active metabolites that prolong the effects (see Table 15). Despite these sometimes very long half lives, the duration of the clinical effects of these agents is usually shorter than the documented half lives as a result of significant distribution of the agents into fatty tissue. As such, the obvious clinical effects can diminish after a few hours. Compounding this feature, even those benzodiazepines with a very long half life have a rapid onset of action (see Table 15). It is therefore relatively common to see “long acting” agents dosed at intervals that are more related to their peak clinical effects than to their actual half lives. It should be noted, however, that the slow accumulation into fatty tissue can then lead to an increase in more subtle effects on gait and cognition over time and benzodiazepines can still be detected in urine tests months after cessation of long term use.[33]

Drug	Approximate Equivalent Dose (mg to Diazepam 5mg)	Time to peak concentration (h)	Approximate Half Life (hours)*
Diazepam	5	0.5-1.5	20-80
Alprazolam	0.5	1-2	6-25
Clonazepam	0.25-0.5	1-4	22-54
Flunitrazepam	0.5	1-2	20-30
Lorazepam	1	2.5	12-16
Nitrazepam	5	2	16-48
Oxazepam	15	1-5	4-15
Temazepam	10	1	5-15
Zolpidem	10	1.5	2
Zopiclone	7.5	1.5	2-5
* Not including active metabolites			

Table 15: Selected Pharmacokinetics of Benzodiazepines (adapted from 31, 32, 33, 34 and 35)

A range of neuroadaptive and pharmacokinetic changes can result in the development of tolerance to some of the effects of benzodiazepines. Tolerance develops to the anticonvulsant effects and probably to the hypnotic and sedative effects, but there does not seem to be any clear evidence of tolerance to the anxiolytic and muscle effects. In addition to tolerance, long term use increases the likelihood of dependence to these agents (see below in Adverse effects).

In addition to changes in the GABA receptor, enhancement of GABA's inhibitory activity results in reduced production of excitatory transmitters and this results in some of the long term side effects of benzodiazepines which include ataxia, memory loss, confusion and possibly depression.

Efficacy of Benzodiazepines

Insomnia

Insomnia is defined as difficulty getting to sleep, staying asleep or having non-restful sleep, despite having enough opportunity for sleep. To meet the criteria for chronic insomnia, people must also have had the issue for four weeks or more and there is some interference with their daytime functioning.[36] Insomnia is one of the most common problems that people present to their GPs with.

While benzodiazepines have been used for decades for insomnia, the studies that support this practice are limited to short term treatment and the overall impact on sleep is moderate at best. Meta-analyses of sedative hypnotic use published in 2005 and 2007 [37,38] identified that:

- The number of patients that would need to be treated with a sedative for one to have an improvement in sleep quality was 13 (95% CI 6.7-62.9).
- The increase in total sleep time with any sedative compared with placebo was 25.2 minutes (95%CI 12.8 to 37.8 minutes)
- There was an decrease in sleep latency (time trying to get to sleep) by approximately 10 minutes
- The mean number of awakenings decreased by 0.63 (95%CI 0.48 to 0.77)

A nursing home study of 178 long term benzodiazepine users compared sleep quality to 122 non-users (mean age 85.5, 75% female, all cognitively intact).[39] They found that users had worse quality sleep in terms of:

- more difficulties falling asleep
- More awakenings overnight

- No difference in total sleep time
- No difference in sleep latency

While it is clear that patients with sleep issues would be more likely to be prescribed benzodiazepines, the study does not support the long term effectiveness of benzodiazepines for this indication.[39]

Guidelines for pharmacological management of insomnia consistently recommend short term use, only after attempts to use non-pharmacological methods which have comparable efficacy to benzodiazepines.[40,41,42] Suggested non-pharmacological therapies that have been shown to be effective for insomnia include relaxation techniques, sleep restriction, exercise and advice on good sleep hygiene.

In older patients with dementia, a Cochrane review found "a distinct lack" of evidence to help guide drug treatment of sleep problems in dementia patients. In particular, they found no trials of drugs that are widely prescribed for sleep problems, including the benzodiazepine and non-benzodiazepine hypnotics.[43]

Anxiety

Anxiety disorders are common and are a spectrum of conditions that vary from mild situational stress responses to severe chronic anxiety with comorbid psychiatric illness. The spectrum of anxiety disorders includes generalised anxiety disorder, panic disorder, obsessive compulsive disorder, post-traumatic stress disorder, phobias and social anxiety disorder.

First-line therapy for all anxiety disorders includes cognitive behaviour therapy (CBT) due to its effectiveness at reducing the symptoms of anxiety in the short and long term. A number of internet-based programs are available (eg moodGYM, This way UP, Mental health online etc) for those with internet access and the ability to use computers are an alternative to face-to-face sessions.[44,45]

Selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) medications are effective across the range of anxiety disorders and are generally suitable for initial pharmacological treatment of anxiety, particularly when there are elements of co-morbid depression. There are, however, few direct comparisons between antidepressants and benzodiazepines.[46,47]

Benzodiazepines are generally regarded by clinical practice guidelines as a short-term therapeutic option for severe, rather than mild anxiety symptoms.[33] They have more benefit for generalised anxiety disorder (GAD), social anxiety disorder and panic disorders than for obsessive compulsive disorder (OCD) or post-traumatic stress disorder (PTSD).[48,49,50] Benzodiazepines can provide symptomatic relief in the early phase of management of anxiety, often while other therapies (eg antidepressants) are taking effect. Note that in some people, the use of benzodiazepines can reduce the efficacy of CBT through the impact on cognition, motivation and wakefulness.

Long-term use, beyond 4 weeks, should be uncommon, as the risk of troublesome side effects and physiological dependence increases with time and dose of benzodiazepine. Some patients with severe and distressing anxiety symptoms may require longer term therapy, and in these cases, close monitoring for the emergence of adverse effects and the development of tolerance and/or dependence should occur regularly.

Adverse Effects of Benzodiazepines

Adverse effects of benzodiazepines have only been adequately studied in the short term, and few studies have specifically addressed adverse effects associated with long term usage. Some of the adverse effects can reduce over time due to tolerance in a similar way to the desired effect of the medication. Most often, subjective feelings of dysphoria and heaviness, along with sedation rapidly subside with continuous treatment.[51]

The impact of the adverse effects of benzodiazepines is greater in certain subgroups:

- Pregnancy: there is increased risk of foetal abnormalities in the first trimester.
- Alcohol consumption: increased risk of excessive sedation and respiratory depression.
- Renal and/or hepatic disease: metabolic clearance of the agents will be compromised.
- Pulmonary disease/sleep apnoea: benzodiazepines are respiratory suppressants
- Older Adults: As a consequence of multiple comorbidities and CNS changes associated with aging, the risk of adverse effects is increased in older adults, especially those over 75 years of age.

In a meta-analysis of sedative hypnotic use in older people published in 2005, Glass et al.[3737] identified that:

- The number needed to harm for sedative hypnotics compared to placebo was 6 (95%CI 4.7-7.1)
- The most common adverse effects recorded were drowsiness or fatigue, headache, nightmares, nausea and other gastrointestinal disturbances.
- Cognitive effects were significantly more common with sedative use than placebo

Effects on Cognition/ Development of Dementia

Long term use of benzodiazepines has been implicated in reduction of cognition,[52] and a case control study has found that there may be an increased incidence of dementia in patients who take benzodiazepines for 6 months or more.[53] Debate regarding the causality in this observational study is ongoing,[54] and it remains unclear whether benzodiazepines increase risk of dementia or are prescribed to combat symptoms (such as anxiety, insomnia and depression) which are related to the neuropathological changes associated with dementia, prior to the diagnosis of dementia being assigned. A recent evaluation of the association between benzodiazepine use and cognitive decline in a cohort of older volunteers followed for seven years has been published.[55] They found that patients who were "users" of benzodiazepines had a lower level of cognitive function but that their rate of decline was no different from non users (see Figure 5).

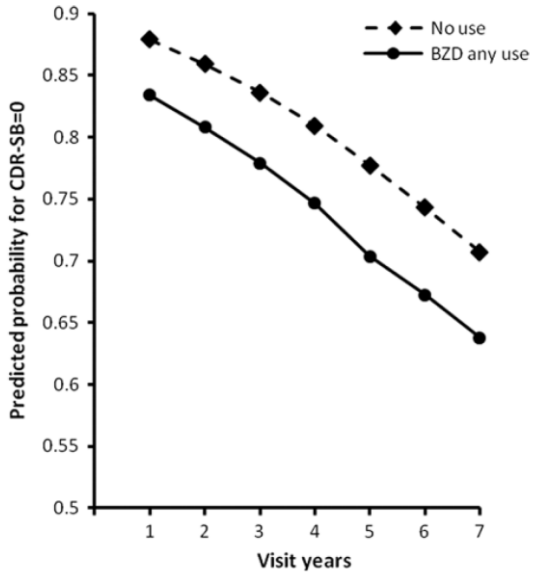


Figure 5: Change in Clinical Dementia Rating Sum of Boxes (CDR-SB) for Benzodiazepine Users vs Non-users (from 55)

In a prospective study of 3434 patients aged 65 or over without dementia at study enrolment, cumulative use of total standardised doses of benzodiazepines use over a 10 year window was examined in relation to development of dementia and cognitive trajectory.[56] Over a mean followup of 7.3 years, 797 (23.2%) people developed dementia (of which 637 were of the Alzheimer's type). Interestingly, there was no relationship between the highest rate of benzodiazepine use (more than 120 standardised doses~ 4 months of daily use) and the development of dementia. Low level use (1-

30 standardised doses) and moderate use (30-120 doses) was, however, associated with an increased risk of dementia with hazard ratios of 1.25 (95% CI 1.03-1.57) and 1.31 (95% CI 1.00-1.71).[56]

Despite these varying results, it is fairly certain, that improvement in a range of neuropsychiatric functions occur after discontinuation of benzodiazepines. [57,58]

Falls

Benzodiazepines are associated with an increased risk of falls. Multiple meta-analyses of the impact of drugs on falls found increased relative risk of falls associated with sedative/hypnotic use. These were reviewed recently and an overall increase in risk of at least one fall during the reported trial periods (often 6 months or less) was between 35% and 60%.[59]

Benzodiazepine Dependence

In addition to the above range of adverse effects, regular benzodiazepine use can result in the development of psychological and physical dependence. Benzodiazepine dependence consists of a strong desire or sense of compulsion to take the agent, difficulty in controlling its use and the presence of a withdrawal state with abrupt cessation. Not all patients who take long term benzodiazepines develop dependence and such patients may find it relatively easy to stop benzodiazepines. For those where withdrawal is likely, slow downward titration of dose may be required (see prescribing practice below) if cessation is intended.

The likelihood of dependence occurring increases with duration of use and is also higher in older patients and those with multiple medical conditions, including depression. There are a number of "indicators" of benzodiazepine dependence and it is suggested that these indicators be monitored for regularly (see Table 16).

Person feels they cannot cope without taking the benzodiazepine
Person has felt ill, had unusual symptoms, couldn't sleep or was anxious as a result of dose reduction
Person takes extra doses when additional stresses are present
Person feels the benzodiazepine is not as effective as it used to be
Person has increased their dose of benzodiazepine
Person has increased their alcohol intake
Person carries their benzodiazepine with them (for "emergency use")
Person has anticipatory symptoms (such as increasing discomfort) leading up to their next dose
Benzodiazepines have had a negative impact on the person's function (work, relationships, coping, memory)

Table 16: Indicators of Possible Benzodiazepine Dependence

Recommended Prescribing Practice

Benzodiazepines may temporarily assist with the symptoms of anxiety and insomnia, but do not address the underlying causes. For many people, improved management of underlying contributing medical conditions (eg COPD, pain) improves anxiety symptoms and sleep.

Prescribing Benzodiazepines

Insomnia

Adequate treatment of insomnia is often difficult and a number of factors may influence the course of the complaint and its treatment. The presence of physical illness, pain and concurrent depression (particularly in chronic insomnia) as well as advanced age and a history of drug and/or alcohol abuse are significant factors to consider.[60]

An accurate history of the nature and functional impact of the sleep complaint may assist in elucidating underlying contributors, causes and potential strategies for management (see Table 17). A sleep diary (eg the NPS sleep diary [61]) and completion of a validated sleep questionnaire (eg the Auckland Sleep Questionnaire [62] or the modified Pittsburgh Sleep Quality Index[63]) may assist in this process. The Auckland Sleep Questionnaire has been tested in a cross-sectional study in primary care. In patients over 75 years of age the most common causes of insomnia were general health problems and depression.[64]

Finding from History	**Potential Strategy**	
Unable to "wind down" at night	Relaxation techniques	Progressive muscle relaxation, deep breathing, pleasant visualisation
Poor lifestyle habits	General sleep hygiene	Consider diet/caffeine intake, exercise patterns, sleep environment
Excessive time in bed awake/ broken sleep	Sleep restriction	Staged increase in sleep with set wake-up time
Learned association between bed and not sleeping	Stimulus control	Restrict bed for sleep (go to bed only when tired, get up if not asleep within 20 min)
Unrealistic expectations of sleep or sleep loss	Cognitive Therapy	Reassurance and modification of distorted beliefs. Often includes elements of relation techniques, stimulus control and sleep restriction.

Table 17: Potential Non-Drug Strategies for Insomnia, Depending on Findings from History. (modified from 65, 66)

A number of medications may contribute to insomnia, and these should be considered as potential contributors to sleep problems (see section on drug induced insomnia). Alternatives may be trialled, or it may be possible to reduce or cease the potentially offending agent.

When a benzodiazepine is required, it is recommended that use be limited to a few weeks and that the medication use is supported by non-drug interventions. [32,33,66,67] A detailed management plan of when to use the agent and when to avoid it, as well as an agreed review date will assist the patient in understanding what to expect from treatment. Explaining that regular use can result in the development of tolerance and/or dependence can assist in arranging an alternate night, or three times a week schedule. A discussion of the interaction of benzodiazepines with alcohol is also prudent at this time.

Resources for patients are available that can assist in supporting non-drug management (and appropriate short term benzodiazepine management) of insomnia and also assist in explaining the risks of long term benzodiazepine use.[68,69]

Anxiety

Anxiety symptoms are frequently secondary to medical or psychiatric conditions and management of these underlying conditions will often improve the anxiety symptoms. In particular, depression, COPD, hyperthyroidism and cardiac issues are related to anxiety symptoms as are a number of medications that are stimulants (see section on drug induced anxiety).

Adequate patient information regarding normal physiological response to stressful life events as compared to incessant worries unrelated to life events can assist in explaining the rationale for not choosing pharmacological treatment. Grading the severity of anxiety will assist in determining initial treatment strategies (see Table 18). Note that ongoing moderate anxiety that is resistant to appropriate management strategies can be considered as severe anxiety.

For mild anxiety, medication use is rarely beneficial and self help or support and counselling techniques are frequently all that is required.

	Severity of Anxiety		
	Mild	**Moderate**	**Severe**
Trigger	Stressful life event(s)	Not always in response to life events	Often unrelated to life events
Degree of Worry	Less than half the time	More often than not	Constant, intrusive worry
Avoidance Behaviour	Absent or infrequent	Common or regular	Constant and marked
Impact on Function	None or slight	Some impairment in work and/or social relationships	Significant impairment in work function, poor or damaged relationships, compromised activities of daily living

Table 18: Grading Severity of Anxiety

For more significant anxiety, cognitive behavioural therapy is recommended. Specific CBT techniques for anxiety include cognitive therapy (addresses the negative thoughts that trigger worry), structured problem solving (addresses feared problems) and anxiety management (helps to manage the physical symptoms of worry).

For more severe anxiety, the addition of short term benzodiazepines to CBT may be effective for relieving some of the somatic symptoms of the anxiety or some of the initial effects of antidepressant agents used to treat the anxiety. They may also be of benefit in situations where rapid symptom control is required

To minimise the risk of dependence developing to benzodiazepine use, the following practical steps are recommended:[70]

- Manage underlying causes and contributors
- Consider behavioural of psychological interventions
- Use only for appropriate indications (for panic disorders seek specialist advice)
- Reserve for short term use (2-4 weeks), assess efficacy at one and two weeks
- Only prescribe to well known patients

Reducing and Ceasing Benzodiazepines

Reduction and cessation of benzodiazepines has been a target of improving medication use for decades with reviews of mis-use of the agents and development of dependence dating back to the early 1980s.

The National Prescribing Service provides a guide for health professionals to assist in stopping benzodiazepine use for people taking them (See Figure 6).[71]

Figure 6: NPS Medicinewise Guide to Stopping Benzodiazepines

A recent review of the clinical evidence and guidelines for benzodiazepine discontinuation found that most studies utilised dose tapering either alone or as part of other interventions (usually psychotherapy). [72,73,74,75,76]

Three studies that utilised a relatively minimal intervention, that of a patient directed letter from their prescriber (with or without a followup consultation), were reviewed together.[77] All three studies reported significant reductions in benzodiazepine use with cessation of the benzodiazepine in 20-35% of subjects in the intervention groups compared to 10-15% of the "usual care" groups at six month followup. A pooled risk difference of 8% (95% CI 3-13%) gave a NNT of 12.[77]

A more intensive strategy, involved the use of a "deprescribing patient empowerment intervention" which involves an education package for patients that describes the risks associated with benzodiazepines and a stepwise tapering protocol.[78] At 6 months, 37.8% of the intervention group

had either discontinued (40/148; 27%) benzodiazepine use or reduced the dose of benzodiazepine (16/148; 10.8%). Usual treatment results were 4.5% (7/155) cessation and 6.5% (10/155) dose reduction (ARR 27%; NNT=3.7). Of interest, in multivariate subanalyses, age greater than 80 years, sex, duration of use, indication for use, dose, previous attempt to taper, and concomitant polypharmacy (10 drugs or more per day) did not have a significant interaction effect with benzodiazepine therapy discontinuation. [78]

A multicentre three arm study used a similar strategy, providing to patients in a structured interview:[79]

- information regarding benzodiazepine dependence and withdrawal symptoms
- information regarding the risks of long term use on memory, cognition, falls and accidents
- reassurance about reducing medication
- a patient self-help leaflet to assist with sleep quality (for those taking benzodiazepines for insomnia).

These authors found that at 12 months, 162 of 369 patients (45%) that received the education (some with further followup) had ceased their benzodiazepine(s), compared with 26 of 173 (15%) in the control group (ARR 30%; NNT 3.3).[79]

It seems relatively clear, therefore, that informing patients taking long-term benzodiazepines has a significant impact on successful deprescribing. The Royal Australian College of General Practitioners (RACGP) has developed patient fact sheets on both the use and cessation of benzodiazepines, along with sample letters for patient mailouts and sample dose reduction strategies for particular agents.[33]

Withdrawal Symptoms

After stopping benzodiazepines, insomnia can return in an exaggerated form and short term changes occur to sleep. Sleep latency is increased, sleep is more disturbed and overall sleep is shorter in duration.[80] Although these changes are of short duration (less than a week), it is common for the recommencement of benzodiazepines to occur in response to these signs. An appropriate support strategy (for example utilising the NPS Fact Sheet [81]) will increase the success of cessation strategies.

About 20% of long term users of benzodiazepines become physically addicted and attempts to withdraw the drug are associated with frank withdrawal symptoms.[82] While it is difficult to predict which patients are more likely to become dependent, those who take higher doses, use high potency compounds (eg alprazolam) and have used the agents for prolonged periods of time are more likely to become dependent.

Withdrawal symptoms include anxiety, insomnia, nightmares, changes to memory and concentration as well as muscle spasms (see Table 19). Patients often experience increases in sensory acuity, often with photophobia and increased sensitivity to everyday sounds.[33,83]

Anxiety symptoms		Distorted perceptions	Major incidents Mainly when high doses are stopped abruptly
Psychological	Physical		
• Anxiety • Panic attacks • Insomnia • Poor memory • Depression • Paranoia • Intrusive memories • Cravings • Nightmares • Excitability • Agoraphobia • Social phobia • Obsessions • Rage, aggression • Irritability	• Agitation • Tremor • Headache • Weakness • Dizziness • Nausea • Vomiting • Diarrhoea • Constipation • Palpitations • Rashes • Tingling, numbness, altered sensation • Fatigue • Flu-like symptoms	• Hypersensitivity to sound, light, touch, taste • Abnormal body sensation eg itching, pain, stiffness, blurred vision, paraesthesia, muscle twitching, tinnitus, burning sensations • Feeling self or world to be abnormal (depersonalisation or derealisation)	• Fits (1–2% of patients) • Delirium (rare) • Transient hallucinations (visual, tactile, auditory) or illusions (rare) • Psychosis (very rare)

Table 19: Acute Withdrawal Affects after Ceasing Benzodiazepines (from 33)

Symptoms generally subside in 2-4 weeks but can be more prolonged. An appropriate tapering schedule can minimise and sometimes avoid these withdrawal effects. It may be required to change the benzodiazepine to diazepam (has a slower elimination) if the agent is being used for anxiety symptoms. A change to diazepam is usually not required if the agent is being used for insomnia. The length of the tapering is influenced by the duration of therapy (see Table 20).

Duration of Benzodiazepine Use	Taper Length
Less than 2 months	May not be required- cease and monitor for rebound/withdrawal
2-6 months	25% per week over 4 weeks
6 months or longer	"TTT" Ten percent reduction over Ten weeks with Terminal Taper (slower reduction for the last steps)
Dose can be considered over a week or two. For example, a 10% reduction may be implemented by asking the person to miss the agent one night in ten, then 2 nights in ten etc.	

Table 20: Recommended Duration of Benzodiazepine Tapering based on Duration of Therapy (adapted from 33,84)

Antidepressants

The use of antidepressants in older people is widespread, with people over 65years old in Tasmania, receiving (on average) 2.1 PBS prescriptions each per year for antidepressants. Across Australia, half as many prescriptions again are dispensed off the PBS, implying that the actual number of prescriptions is more like 3 per person. Given the majority of these prescription provide enough medication for 6 months of therapy, either the use of these agents is almost ubiquitous in this age group or many prescriptions are not completely filled.

Given the widespread use of these agents in this age group, ensuring that they are effective and are not causing adverse effects becomes a significant issue. The agents are optimally provided in conjunction with psychotherapy, however, the majority of older people that are treated receive only antidepressant medication.

Clinical Pharmacology of Antidepressant Agents

The neurotransmitters dopamine, noradrenaline and sertraline are thought to be associated with depression, and the majority of effective antidepressant agent impact on one or more of these neurotransmitters. While more recent antidepressants are relatively specific in their impact on receptors, some agents have a broad profile of receptor affinity and therefor impact on monoamine and other neurotransmitter concentrations. These variations are responsible for the differences in adverse effects and possibly efficacy between the agents (see section on antidepressant adverse effects). A schematic of the clinical symptoms associated with blockade and reuptake inhibition of some of the common neurotransmitters is shown in Figure 7 and the relative affinities of some of the available antidepressants are shown in Table 21.[85]

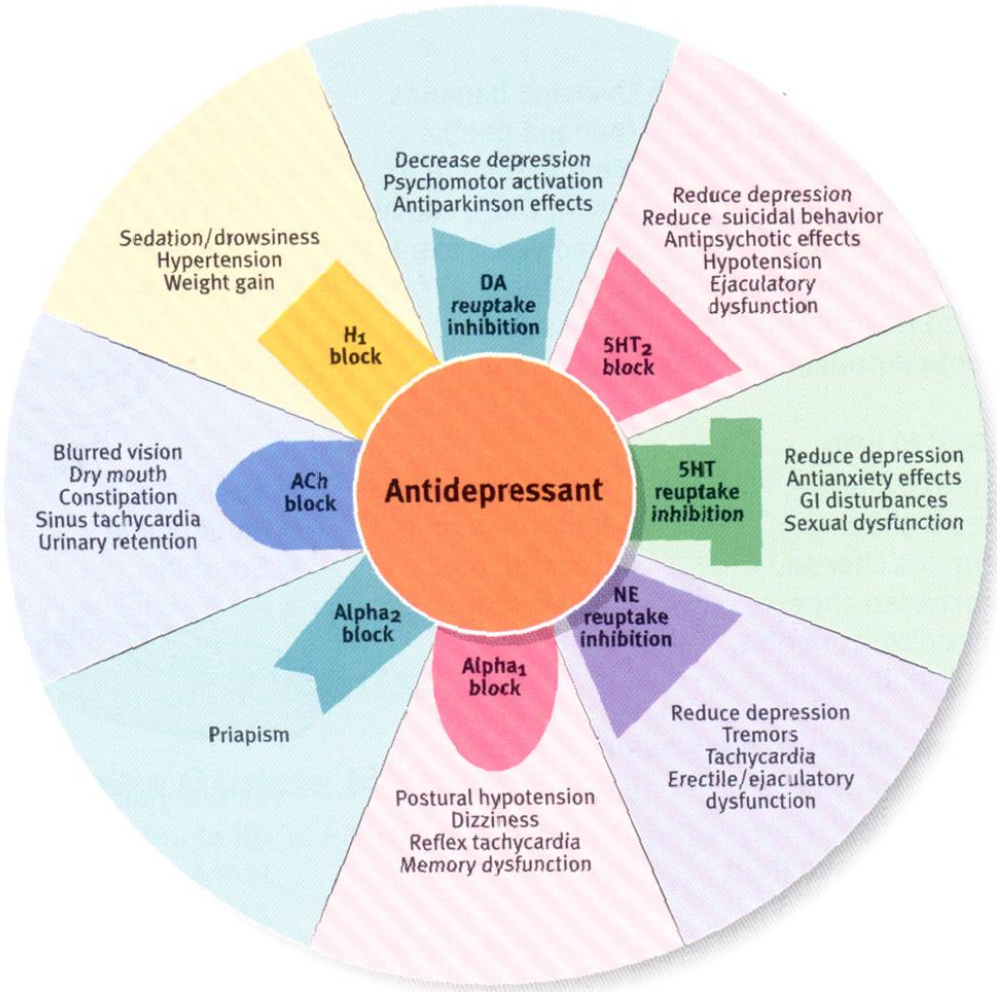


Figure 7: Clinical Symptoms Associated with Blockade and Reuptake Inhibition of Various Neurotransmitters.

Drug	Relative Potencies		
	Serotonin	Noradrenaline	Dopamine
Amitriptyline	+++	++	-
Citalopram	++++	-	-
Desipramine	++	++++	-
Fluoxetine	+++	+	-
Fluvoxamine	+++	+	-
Imipramine	+++	++	-
Nortriptyline	++	+++	-
Paroxetine	++++	++	-
Sertraline	++++	+	+/-
Venlafaxine	++	+	+/-

Table 21: Relative Affinities of Some Antidepressants for Serotonin, Noradrenaline and Dopamine (from 85).

The starting doses, maximum doses and some practical comments relating to the antidepressants commonly used in Australia are listed in Table 22.

Medication	Starting Dose	Maximum Dose	Comments
Tricyclic Antidepressants			
Amitriptyline	50 mg once/day	150–300 mg	Causes weight gain, strong anticholinergic properties
Clomipramine	25 mg once/day	100–250 mg	
Doxepin	25 mg once/day	150–300 mg	Causes weight gain, strong anticholinergic properties
Imipramine	25 mg once/day	150–300 mg	May cause excessive sweating and nightmares
Nortriptyline	25 mg once/day	50–150 mg	
Trimipramine	50 mg once/day	150–300 mg	
MAOIs			
Phenelzine	15 mg tid	45–90 mg	Causes orthostatic hypotension
Tranylcypromine	10 mg bid	30–60 mg	Causes orthostatic hypotension Has amphetamine-type stimulant effects and modest abuse potential
SSRIs			
Citalopram	10 mg once/day	20 mg	Lower potential for drug interactions because it has less effect on CYP450 isoenzymes Risk of QT-interval prolongation that limits doses to ≤ 20 mg/day in older people
Escitalopram	10 mg once/day	10–20 mg	
Fluoxetine	10 mg once/day	20–60 mg	Has very long half-life, and active metabolite with a longer half life Less likely to cause discontinuation symptoms Multiple drug interactions
Fluvoxamine	50 mg once/day	100–200 mg	Multiple drug interactions
Paroxetine	20 mg once/day 25 mg CR once/day	20–50 mg 25–62.5 mg CR	Multiple drug interactions Strong anticholinergic properties Of SSRIs, may cause the most weight gain
Sertraline	50 mg once/day	50–200 mg	Of SSRIs, has highest incidence of GI problems
Serotonin-norepinephrine reuptake inhibitors			
Desvenlafaxine	50 mg once/day	50–100 mg	May increase BP or HR (dose dependent)
Duloxetine	20 mg bid	60–120 mg	Modest dose-dependent increase in BP May cause mild urinary hesitancy in males
Venlafaxine	25 mg tid 37.5 mg XR once/day	75–375 mg 72–225 mg XR	Modest dose-dependent increase in BP Dual norepinephrine and 5-HT reuptake effect at about 150 mg
Serotonin modulators (5-HT_2 blockers)			
Mirtazapine	15 mg once/day	15–45 mg	Causes weight gain Causes sedation at low doses
Melatonergic antidepressant			
Agomelatine (5-HT_{2C} receptor antagonist)	25 mg once/day at bedtime	25–50 mg	Potential for serious liver injury (stop if serum transaminases increase to > 3 times normal)

Table 22: Antidepressants, Doses and Relevant Practical Comments (adapted from 86,87)

Efficacy of Antidepressants in Older Patients

The range of signs and symptoms associated with depression is considerable, and determining where there has been a clinically significant response to treatment requires close assessment of the individual patient and changes to function as well as mood. When interpreting clinical trials of antidepressants, caution is required in relation to the methods used. This is because the level of change in various evaluation tools that corresponds to a clinical response can vary between studies.

Antidepressant medications alone have only moderate efficacy in depression with an approximate response rates (usually classified a s 50% reduction in score of whatever evaluation tool was used) of 48–50% compared with 30–32% for placebo (NNT 5–7) [88,89] Response is often, however, incomplete and many patients continue to have some clinically important continuing symptoms.[89] Determining whether there has been a clinical response is often multifaceted, and relief of particular symptoms (as part of a partial response) may be more important to some patients than others.

The benefits for antidepressants over placebo appear to increase with duration of depression and there is some evidence that antidepressants are more effective in patients with more severe depression.[90] There are 'threshold zones' where benefit is uncertain(see Figure 8).[89]

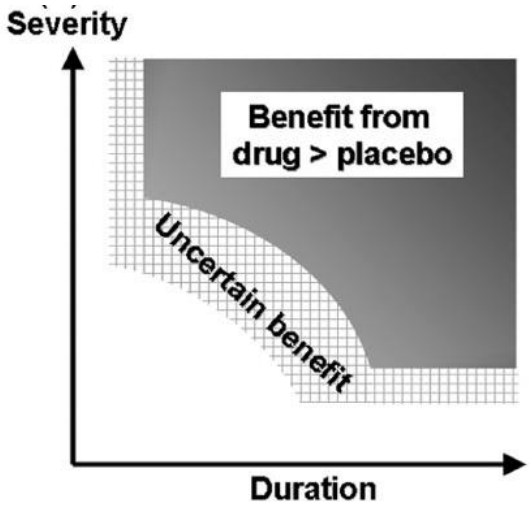


Figure 8: Hypothesised Benefit from Antidepressant Drug Treatment compared to Depression Severity and Duration. (from 89)

The finding of increased response with increased severity of depression has been questioned due to methodological issues with the meta-analysis that came to this conclusion.[91] Recently, the principle was retested using patient-level data and also re-undertaking a meta-analysis of trial-level data from 34 randomised placebo controlled trials (n = 10 737) from the NEWMEDS registry.[92] The authors found that the trial-level data supported previous findings (ie response was related to initial severity), but the patient-level data did not (ie initial severity and outcomes were similar in treatment and placebo groups).[92] Thus, this issue remains unclear, at least in the literature.

Specific information on depression in older people is gained from studies that have lower limited age thresholds. A meta-analysis of such trials compared trials with different age cutoffs. [93] They defined response as a 50% or greater reduction in depression scores and found that odds ratio for response for all 74 adult studies that they examined was 1.42 (95%CI 1.35-1.49), meaning there was a 42% response rate. When the studies were separated into those for adults (all patients less than 65 years old), late life depression (all patients 55 years old or more) and older late life depression (all patients 65 years old or more), they found that the older late life groups had a lower response rate than the overall adult groups (see Figure 9).[93]

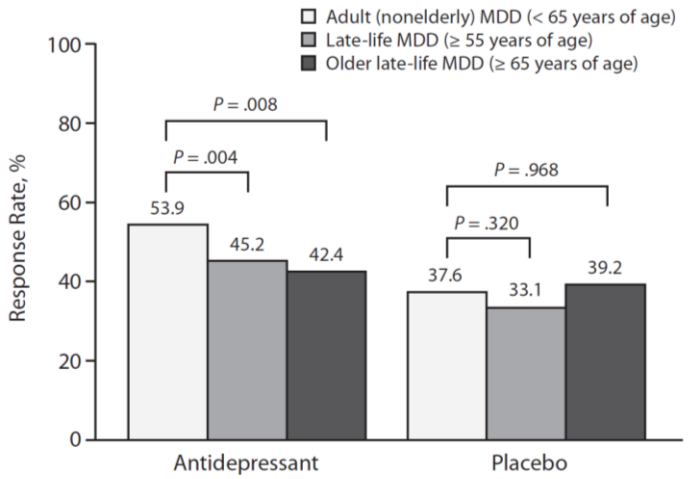


Figure 9: Response rate to antidepressants in adults (<65yo), Late Life (55 yo or more) and Older Late Life (65 yo or more) depression. (From 93)

Of interest, they reported that the response rate in studies of over 65 year olds did not differ from the response rate with placebo. They postulated that the lack of difference with placebo may be related to the severity/chronicity of depression, the possibility of cognitive issues in the older age group or the possibility that a longer time to response may be evident in the older age groups (many of the trials were of only 6 to 8 weeks duration).[93] A previous review of the efficacy of second generation antidepressants in older patients adds some support to the notion that longer response times are needed.[94] They found that response rates were higher for trials that had a longer observation period (55% for 10 to 12 week trials; 38% for 6 to 8 week trials).[94] In a 12 week open label study of venlafaxine in older adults, factors that increased the likelihood of non-response were greater baseline severity of disease, longer episode duration, less subjective sleep loss, more guilt and more work/activity impairment.[95]

Nine recent trials of antidepressants in older patients have been examined in a systematic review (see Figure 10).[96]

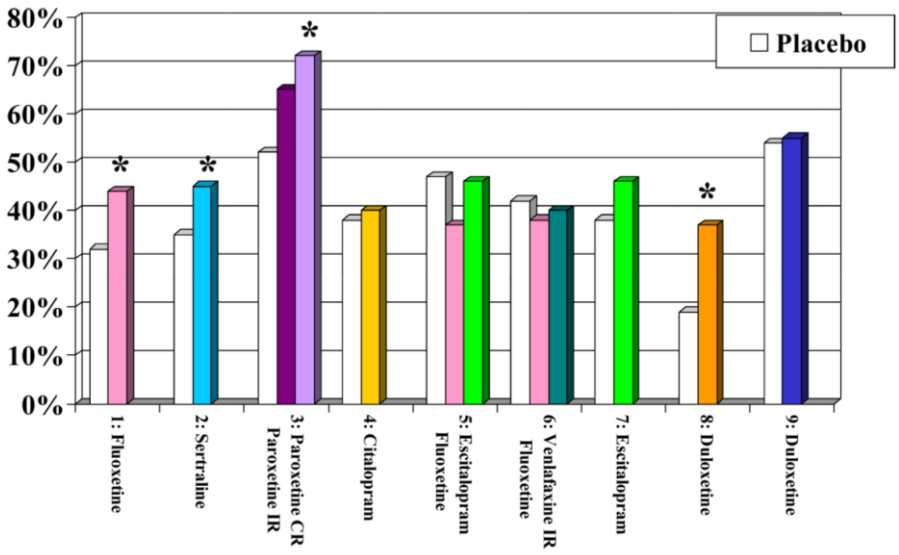


Figure 10: Response rates in Trials of Antidepressants for Older Patients with Depression. (From 96).

They found that some agents showed no difference to placebo in this age group, and they proposed a sequence of selection of agents based on previous US guidelines and the results of these and other trials (see Table 23). Note that bupropion is not available as an antidepressant in Australia.

Stepwise Antidepressants for Geriatric Major Depression (6 week trial)	**Alternatives** (4-8 week trial)
Step 1 Escitalopram	sertraline, duloxetine
Step 2 for minimal or non-response: Switch to duloxetine	venlafaxine, desvenlafaxine
Step 3 for minimal or non-response: Switch to nortriptyline	Bupropion*
Step 2-3 for partial response : Augment antidepressant with lithium or an atypical antipsychotic	combine SSRI or SNRI with mirtazapine or bupropion
Not approved for depression treatment in Australia	

Table 23: Suggested Treatment Sequence for Late-Life Depression (From 96)

The minimal response to these agents and the increased risk of adverse effects (see below) in older patients has prompted many commentators to suggest that antidepressant use in older people may no longer be appropriate.[88,97,98,99,100,101]

Clearly, a blanket suggestion that these agents should not be used in older people is not appropriate, and clinicians are urged to consider individual responses to treatment in order to balance any ongoing benefit again possible or actual risks of therapy.

Efficacy of Antidepressants in Patients with Dementia

Depression is common in patients with dementia, but the evidence base for antidepressant treatment in this patient population is sparse. A metaanalysis of trials published in 2011 was only able to accumulate data from seven trials with a total patient population of 330 people (six of the trials had fewer than 50 participants).[102] The authors were unable to demonstrate the efficacy of antidepressant agents in terms of either response rates or remission rates. They also stated that methodological issues such as underpowering, variable trial methods and differences in antidepressants confounded the finding even further.[102] A more recent meta-analysis that focussed purely on SSRIs has been published.[103] They too, were unable to show any statistical differences between SSRIs and placebo in terms of depression scores or cognition scores. [103]

The largest randomised trial in the most recent meta-analysis was of sertraline, mirtazapine or placebo for depression in patients with Alzheimer's disease. [104,105] These authors randomised 326 patients to sertraline (107), mirtazapine (108) or placebo (111) and were unable to demonstrate any differences between the three groups on any outcomes at 13 and 39 weeks after commencement of the agent. The primary outcome assessed was the Cornell Scale for Depression in Dementia (CSDD) score, but other outcomes included cognition, activities of daily living, behavioural, quality of life and carer burden scores. Their conclusion was "*Because of the absence of benefit compared with placebo and increased risk of adverse events, the present practice of use of these antidepressants, with usual care, for first-line treatment of depression in Alzheimer's disease should be reconsidered*."[104] It is interesting to note that there was an improvement in depression scores in all three groups, including placebo (see Figure 11**Error! Reference source not found.**). The fact that the patients were all recipients of care from specialist old-age psychiatry services (offering psychosocial and environmental interventions such as behavioural therapy and exercise) is likely to have impacted on the results. In addition, patients generally had milder depression (the average commencing CSDD score was approximately 13, with almost 50% of patients having scores of 8 to 11) and milder depression may be less likely to respond to antidepressant therapy.

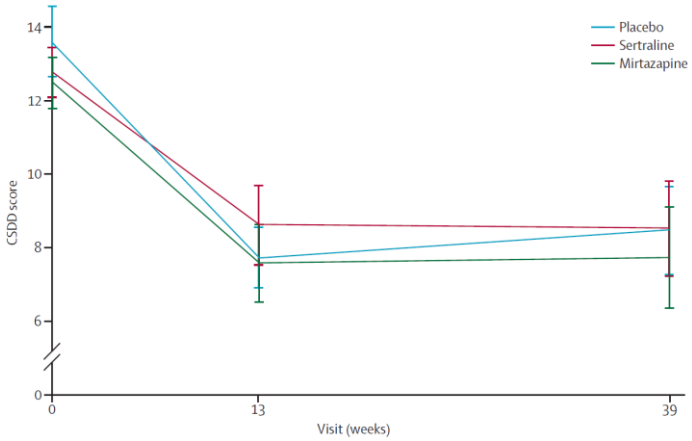


Figure 11: Cornell Scale for Depression in Dementia Scores from Reference 104.

While this study adds some understanding to the effects of commencing an antidepressant in patients with dementia, a more recent discontinuation study of dementia patients with behavioural and psychological symptoms of dementia ceasing antidepressants is of interest.[106] These authors randomised 128 dementia patients taking and antidepressant (who did not have a depressive disorder) to continuation or cessation of the antidepressant (placebo controlled). At 25 weeks after cessation of the antidepressant, the CSDD score was increased by ~2 points in patients who discontinued the agents. Of interest, they found that the neuropsychiatric Index (NPI) score was also increased somewhat, but the study did not have sufficient power to detect a statistical difference (NPI scores 22.5 in discontinuers, 14.7 in continues, p=0.056).[106]

Antidepressants for Behavioural and Psychological Symptoms of Dementia

Antidepressants may have some benefits in the treatment of agitation in people with dementia and have been suggested as a safer alternative to antipsychotics for this purpose.[107] Indeed, a trial of citalopram versus risperidone in 103 patients with dementia showed that agitation scores were improved by citalopram and not by risperidone.[108]

A larger, more recent, study of citalopram on agitation in Alzheimer's disease has been published.[109] The study enrolled 186 participants diagnosed with probable Alzheimer's disease (Mini Mental State Examination [MMSE] score between 5 and 28 points) that experienced clinically significant agitation to receive a target dose of 30mg of citalopram or placebo over 9 weeks of follow-up and measurement. The results of the trial are multifaceted with some benefits to citalopram use, and some significant potential risks associated with its use.

In terms of benefit, there was an improvement in agitation scores (see Figure 12) in the citalopram group. The improvement in the scores was modest, and seemed to occur rapidly (within 3 weeks), implicating a mechanism other than the antidepressant effect of the citalopram. Further analysis by the same research group) has indicated that some of the improvement in the scores was due to a sedative effect of the citalopram.[110] As with other studies, there was an improvement in the scores for patients receiving placebo as well.[111]

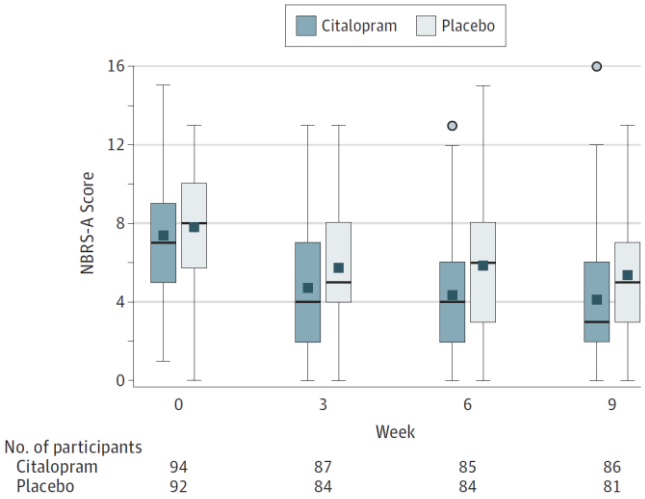


Figure 12: Neurobehavioral Rating Scale (NBRS)-Agitation Subscale scores from the CitAD Study (109)

There was also a slight improvement in the Clinical Global Impression of Change scale (see Figure 13) for patients receiving citalopram compared to placebo.

Figure 13: Impact of Citalopram on Clinical Global Impression of Change (modified from 109).

In terms of adverse outcomes, there was an decrease in cognitive scores in the citalopram group and an average increase in the QTc interval of 18ms. It should be noted that in the USA, there is a ”black box” warning for use of doses of citalopram above 20mg for patients over 60 years of age because of the cardiac conduction issues.[112]

Interpretation of the results of this study have been enthusiastic and there has been support for SSRIs being “*an effective pharmacologic intervention*”.[113] It seems, however, that antidepressants, antipsychotics, mood stabilisers and cholinesterase inhibitors may all have similar, moderate effects in mild to moderate agitation in patients with dementia. As such, a thorough assessment of the situation with careful consideration of the risks or the treatment and the level of distress caused by the symptoms may assist in deciding which (if any) treatment is required.

Adverse Effects of Antidepressants in Older Patients

Although antidepressants have a range of adverse effects, it should be noted that depression is also associated with a number of significant medical consequences, independently of whether

antidepressant agents are used. Immune system changes and dysfunction of the hypothalamic-pituitary-adrenal axis associated with depression can lead to end organ damage.[97] Adverse effect reporting from observational studies needs to be interpreted with caution, and these are effectively comparing depressed patients taking antidepressants with non-depressed patients not taking antidepressants and it is difficult to determine whether the differences are due to depression or the antidepressant.

Notwithstanding this, a range of common adverse effects are associated with antidepressant use, often leading to a reduction in adherence to the regimen by patients commencing (or increasing) antidepressants. Quite rapid tolerance to many of the adverse effects associated with antidepressants occurs, and reassuring patients that are newly prescribed these agents that some of the adverse effects may attenuate can assist in completing a trial of the agent (see Figure 14).

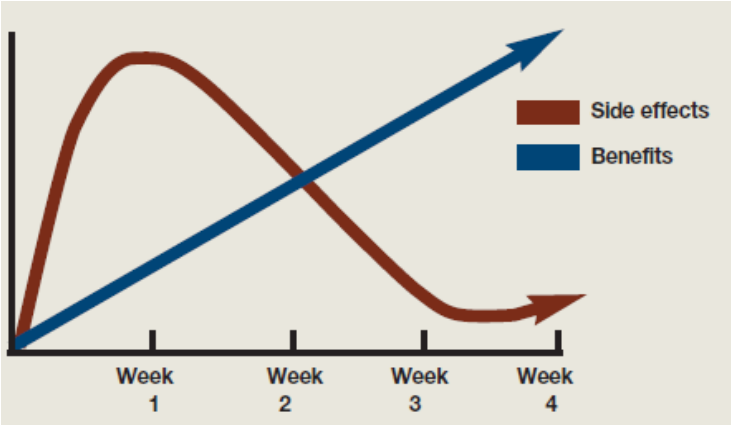


Figure 14: Time Course of Side Effects and Benefit from Antidepressants

A number of adverse effects are “class” adverse effects, with some variation between different agents within the classes for particular adverse effects (see Table 24).

Class	Agent	More Common Adverse Effects	Less Common or Rare Side Effects
Selective Serotonin Reuptake Inhibitors	Citalopram Duloxetine Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline	Insomnia Agitation Anxiety Constipation Diarrhoea Nausea Tremor Hyponatraemia	Serotonin syndrome Decreased appetite Bruxism Extrapyramidal reactions Postural hypotension
Tricyclics	Amitriptyline Dothiepin Doxepin	Arrhythmias Confusion/Disorientation Extrapyramidal reactions Hypotension Tremor Blurred vision Constipation Urinary retention Paraesthesia	Anxiety Ataxia Blood dyscrasias Hallucinations Gynaecomastia Hypomania SIADH Seizures
Serotonin and Noraderenaline Reuptake Inhibitors	Venlafaxine Desvenlafaxine	Agitation Anxiety Confusion Depersonalisation Hypertension	Mania/Hypomania Blood dyscrasias QT prolongation Serotonin syndrome Seizures SIADH
Tetracyclics	Mirtazapine	Hepatic Impairment Joint/muscle pain Increased appetite Drowsiness (low dose) Dizziness/Postural Hypotension Tremor Weight gain Nausea	QT prolongation Agitation Anxiety Blood dyscrasias Hyperkinesia Paraesthesia

Table 24: Adverse Effects of Selected Antidepressants (from 16,97,99,101,

Considerations in Older People

As previously outlined in the section on mental health drugs, older people have an increased sensitivity to the central effects (both therapeutic and toxic) of centrally acting agents. Older patients therefore often require lower dosage and more gradual dose increases to avoid toxicity, because of slower metabolic rates and/or excretion and an increased ratio of fat to lean tissue.

Older patients also exhibit increased sensitivity to anticholinergic effects, such as urinary retention (especially in older men with prostatic hypertrophy), anticholinergic delirium, and increased sedative and hypotensive effects. Tricyclic antidepressants and paroxetine in particular have strong anticholinergic properties and may cause confusion in older patients, and should be used with particular care in those with impaired hepatic or renal function, or with cardiovascular disease.

Recommended Prescribing Practice

Antidepressants are generally considered to be of similar efficacy, have a reasonably wide safety margin and some differences adverse effect profiles (see earlier) and in their potential for interaction with concurrently administered drugs (see section on pharmacokinetic changes). Some of

the factors that are commonly used to differentiate between the agents (and therefore when to use which agents) are shown in Table 25.

Drug	Sedation	Activation	Drug Interactions	Anticholinergic Properties
SERTRALINE	0	++[2]	0	
ESCITALOPRAM	+	+[2]	+	
VENLAFAXINE		+++[1]	+	
AMITRIPTYLINE	+++		+	+++
MIRTAZAPINE	++++		+	
DESVENLAFAXINE		++[1]	+	
CITALOPRAM		+	++	
FLUOXETINE	0	++[2]	+++	
DULOXETINE		++	+	
PAROXETINE	+++	+[2]	+++	+++
DOTHIEPIN	++		+	++
FLUVOXAMINE	+++	+[2]	++	
DOXEPIN	+++		+	++
NORTRIPTYLINE	+		0	+

[1] Individual and dose dependent
[2] Often settles a few weeks after commencement
0=none, + = mild, ++ = moderate, +++ = significant, ++++ = severe

Table 25: Relative Properties of Commonly Prescribed Antidepressant Agents

Despite the absence of clear clinical data for treatment of depression in later life, treatment guidelines have been created on the basis of expert opinion.[86,114,115] A suitable strategy is outlined in Figure 15.

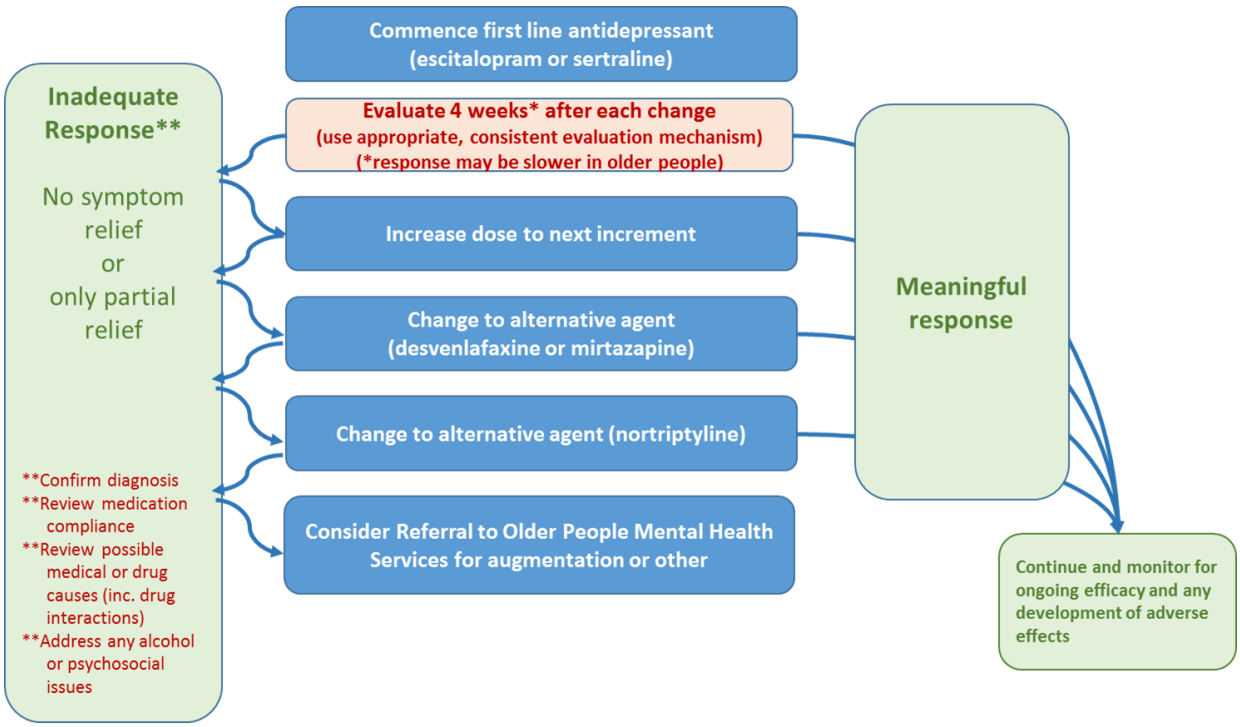


Figure 15: Recommended Prescribing of Antidepressants in Older People

An important component of the flowchart above is the response to a partial response that does not fully meet the patients goals.

A review of the diagnosis is often warranted, as depression as a part of unrecognised bipolar disorder may respond better to mood stabilisers or quetiapine compared to true antidepressants. Many older patients in particular have early, undiagnosed cognitive decline which may present with features similar to depression.

Medication compliance with antidepressants is often an issue, particularly in the early phase of treatment, when side effects can be more prominent. Clear information for patients commencing on (or increasing the dose of) antidepressants helps to support compliance during this initial phase.

Continuing Use of Antidepressants in Older People

There are, however, some situations where use of the agents may no longer be required.

Patients who have a clear past history of major depression who go on to develop dementia or other neurodegenerative conditions may worsen if the agents are ceased.

Patients where the antidepressant is commenced as part of the management of symptoms associated with dementia should have the efficacy reviewed (with respect to both depression and BPSD) in order to justify continuation.

Older patients with multiple relapses of depression are more likely to relapse if antidepressants are ceased (often as a result of multiple co-morbidities). Ongoing monitoring of efficacy and development of adverse effects in this age group is recommended.

Antipsychotics

Antipsychotics are used for a range of serious mental health disorders and much of their prescribing (at least initially) is through psychiatric specialists. This section focusses on the area where GPs have a significant role in management, being the management of behavioural and psychological symptoms of dementia.

Clinical Pharmacology of Antipsychotic Agents

All antipsychotic agents reduce the impact of dopamine in the central nervous system. Excessive dopamine is thought to be related to the psychotic and other positive symptoms of schizophrenia in the mesolimbic pathway. Schizophrenia is also often associated with negative symptoms which are thought to be mediated through altered dopaminergic transmission in the mesocortical pathway.

A number of atypical (or second generation) antipsychotic agents have been developed that affect both of these pathways and therefore have impact on both positive and negative symptoms associated with schizophrenia. There are differences between first and second generation antipsychotics agents in relation to their relative affinities for different dopamine receptor subtypes, in the rates of dissociation from the D2 receptors and also in terms of their impact on other receptor subtypes, particularly $5HT_2$.[116]

Efficacy of Antipsychotics

Many randomised trials have attempted to demonstrate efficacy of antipsychotic agents in dementia patients with behavioural and psychological symptoms of dementia. Most of these studies have small sample sizes and the majority monitor patients for a maximum of 12 weeks.

Older agents have been examined in a systematic review and a meta-analysis covering 12 trials was unable to find any clear evidence for efficacy of conventional antipsychotics (eg perphenazine, thioridazine, haloperidol).[117]

The Clinical Antipsychotic Trial of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) was a 42 site double blind placebo controlled trial of 421 patients with behavioural and psychological symptoms of dementia. BPSD symptoms included psychosis, aggression, or agitation and patients were randomised to a flexible dose regimen of risperidone, quetiapine, olanzapine or placebo for up to 36 weeks. [118] The main outcome was time to discontinuation. No significant differences were found in overall time to discontinuation or in clinical improvement between treatment with antipsychotics and placebo.[118] The study allowed for a change between treatments at the physician's discretion after a 12 week period (termed end of Phase one). An analysis of the Phase one results indicated that antipsychotic agents may be more effective for particular symptoms such as anger, aggression and paranoid ideas.[119]

A 2006 Cochrane review of the use of atypical antipsychotic agents found that risperidone and olanzapine had a beneficial effect on aggression symptoms in approximately 20% of patients.[120] A systematic review of 22 studies of the use of antipsychotics (and 7 studies of other agents) for patients with dementia in long term care concluded that there is limited evidence to support the use of antipsychotic agents in this population.[121]

While some improvement in BPSD may occur during the initial phases of treatment with antipsychotics, there is no evidence that long term treatment changes outcomes. The frequency of behaviours is also a factor in whether there will be a noticeable response. Treatment with antipsychotics is more likely to have a noticeable impact on behaviours that recur four or more times per week than less frequently.[122]

Some behaviours are not changed by antipsychotics in the intermediate to long term. These include wandering, calling out, urinating in inappropriate places, hypersexuality (see Table 26).

Behaviours that May Respond	Behaviours that Respond poorly
Hallucinations	Apathy
Delusions	Wandering
Persistent angry states	Calling out
Persistent extreme anxiety	Inappropriate toileting
Persistent aggression	Low mood
	Hypersexuality

Table 26: Types of Behaviour Associated with Dementia and Response to Antipsychotics (from 117,118,121,122)

Indeed, a study of withdrawal of antipsychotic agents in 102 dementia patients who had been taking antipsychotics (at least 100mg chlorpromazine equivalent or 0.5mg risperidone) for BPSD for 3 months or more found that cessation did not impact on neuropsychiatric index significantly.[123]

A Cochrane review of withdrawal vs continuation of chronic antipsychotic drugs for BPSD in older people with dementia was published in 2013.[124] They found that overall, in seven of nine trials, antipsychotics could be withdrawn without a significant effect on most outcomes. In particular, behavioural symptoms, as measured by the neuropsychiatric index were not influenced in most people.[124] They found some evidence that patients with more severe BPSD (as indicated by a neuropsychiatric index score over 14) could benefit from continuing antipsychotic treatment. They also found that some patients who previously had psychotic features or severe agitation may relapse after discontinuation.[124]

There are a number of National and International guidelines and recommendations for use of antipsychotics in patients with dementia.[125,126,127 ,128,129,130, 131,132,133] It should be noted that there are significant similarities between these guidelines and the use of these agents is limited to selected situations for short periods of time.[134]

Australian clinical practice guidelines have been recently published.[135,136] Their recommendations that are specific to the use of antipsychotic agents (89-91) are shown in Table 27.

Recommendation	Evidence Base for Recommendation
89: People with Alzheimer's disease, vascular dementia or mixed dementias with mild to-moderate behavioural and psychological symptoms of dementia should not usually be prescribed antipsychotic medications because of the increased risk of cerebrovascular adverse events and death.	Moderate
90: As far as possible, antipsychotics should be avoided in people with Dementia with Lewy Bodies due to the risk of severe untoward reactions, particularly extrapyramidal side effects. Acetylcholinesterase inhibitors could be considered. If antipsychotics are used for severe behavioural and psychological symptoms of dementia, atypical or second generation antipsychotics with low propensity to cause extrapyramidal side effects should be used; quetiapine and olanzapine are considered to have the best tolerability. Healthcare professionals should use low dosage and closely monitor for adverse effects.	Practice Point- Expert Opinion
91: People with dementia and severe behavioural and psychological symptoms of dementia (i.e., psychosis and/or agitation/aggression) causing significant distress to themselves or others, may be offered treatment with an antipsychotic medication. Risperidone has the strongest evidence for treating psychosis. Risperidone and olanzapine have the strongest evidence for treating agitation/aggression, with weaker evidence for aripiprazole. The following conditions should also be met: • There should be a full discussion with the person with dementia and their carers and family about the possible benefits and risks of treatment. In particular, cerebrovascular risk factors should be assessed and the possible increased risk of stroke/transient ischaemic attack and possible adverse effects on cognition discussed. • Target symptoms should be identified, quantified and documented. • The effect of comorbid conditions, such as depression, should be considered. • The choice of antipsychotic should be made after an individual risk–benefit analysis. • The dose should be initially low and titrated upwards if necessary. • Monitoring for adverse effects including the metabolic syndrome should occur. • If there is no efficacy observed within a relatively short timeframe (usually one to two weeks), treatment should be discontinued. Treatment should be reviewed every four to 12 weeks, considering the need for antipsychotics and possible cessation of medication. Review should include regular assessment and recording of changes in cognition and target symptoms.	Moderate

Table 27: Australian Clinical Practice Guideline Recommendations relating to Antipsychotic Use (From 136)

The Dementia Behaviour Management Advisory Service provides a comprehensive guide to non—pharmacological and pharmacological management of specific behaviours commonly encountered in dementia. The guide is now available as a phone/device application (http://dbmas.org.au/rModerateesources/bpsd-guide-app/).[137]

One important factor to consider is the role of inadequately managed pain in patients with dementia. Pain in patients with impaired language and dementia may manifest as agitation. More

effective treatment of undiagnosed pain may contribute to the overall management of agitation in patients with dementia.[138,139,140]

Adverse Effects of Antipsychotics

Antipsychotics have a range of metabolic, cardiac, movement and CNS adverse effects. Metabolic adverse effects include weight gain, diabetes and the development of the metabolic syndrome. Many antipsychotic agents also prolong QT interval and can exacerbate or precipitate arrhythmias and syncope. Movement disorders, which can result from or be exacerbated by antipsychotics, include a range of extrapyramidal symptoms from acute dystonic reactions, through akathisia, parkinsonism and tardive dyskinesia. CNS adverse effects can be variable, with somnolence, cognitive worsening and occasionally abnormal gait and seizures.

Akathisia is an extrapyramidal syndrome that may be induced by antipsychotic and other anti dopaminergic agents. It is characterised by an "inner restlessness" that makes the patient feel anxious, agitated and is often associated with and urge to move, manifesting as pacing, leg movements or leg rubbing. This adverse effects typically commences 3-8 weeks after initiation or dose increase of an antipsychotic agent. The relative frequency of extrapyramidal and other common, less serious adverse effects for the different antipsychotic agents is shown in Table 28.

	Extrapyramidal	Sedation	Weight gain	Hyperglycaemia	Anticholinergic	Orthostatic hypotension
Atypical antipsychotics						
Risperidone	●●	●● initially	●●	●●	●	●● initially
Quetiapine	●*	●●●	●●	●●●	●●	●●
Olanzapine	●	●●●	●●●	●●●	●●●	●
Clozapine	●	●●●	●●●	●●●	●●●	●●
Amisulpride	●●*	●	●	●	●	●
Aripiprazole	●	●	●	●	●	●
Ziprasidone	●	●●	●	●	●	●●
Typical antipsychotics						
Haloperidol	●●●	●	●●	●●	●	●
Chlorpromazine	●●	●●●	●●●	●●●	●●●	●●●

Approximate frequency of adverse effects: ● (<2%) = negligible or absent; ● (>2%) = infrequent; ●● (>10%) = moderately frequent; ●●● (>30%) = frequent. * rarely a problem at usual therapeutic doses

Table 28: Frequency and Severity of Adverse Effects with Antipsychotic Agents (from 141)

In addition to these adverse effects, there are serious concerns regarding the use of antipsychotics in patients with dementia in terms of increased mortality, increased strokes and increased falls.

Increased Mortality

In 2005, the United States Food and Drug Administration analysed 17 trials of atypical antipsychotic use in dementia (some of which were unpublished) and showed an increased relative risk of death of approximately 54-70% (an absolute increased risk of 1-2% per year; NNH 50-100).[142] The increased mortality was mainly due to vascular or infectious causes.

The FDA warning was subsequently extended to cover all antipsychotics (including the older agents) following retrospective population-based studies that demonstrated that typical antipsychotics also showed a similar increased risk of death. [143, 144]

Mittal et al. reviewed the evidence relating to antipsychotic associated cerebrovascular events and mortality risk.[145] The increase in mortality was 1.2-1.6 fold higher when antipsychotics were used.

Older age, male gender, severe dementia and functional impairment were all associated with a higher risk of death. [145]

Long-term mortality follow-up data from the DART-AD study indicated that discontinuation of antipsychotics was associated with reduced mortality at 12, 24, and 36 months.[146]

A retrospective cohort study using national data from the US Department of Veterans Affairs for patients ≥65 years old with dementia, beginning outpatient treatment with an antipsychotic (risperidone, olanzapine, quetiapine, or haloperidol) or valproic acid examined mortality. [147] They found the following rates of mortality:

- Haloperidol : 45.8 deaths per 100 person years: RR 1.54 (95%CI 1.38-1.73)
- Risperidone : 27.5 deaths per 100 person years : RR 1.00 (reference)
- Olanzapine : 27.1 deaths per 100 person years : RR 0.99 (95%CI 0.89-1.10)
- Valproate: 21.0 deaths per 100 person years : RR 0.91 (95%CI 0.78-1.06)
- Quetiapine: 18.6 deaths per 100 person years : RR 0.73 (95%CI 0.67-0.80)

The same research group more recently updated this study in order to determine absolute risks.[148] They examined the 180 day mortality of patients for the same five antipsychotics and also for antidepressants against similar patients matched for age, dementia diagnosis, race, presence of delirium, and comorbidity score. All patients had no prescription use of any of the study agents for the six months before the study (ie they were all new users of the agents). Death rates are shown in and as can be seen, haloperidol and risperidone have a very low number needed to harm. For these two agents a new prescription for less than 30 patients would result in an additional death within six months.

Medication	Deaths in 180 days		NNH n (95%CI)
	Users n (%)	Non-Users n (%)	
Haloperidol	398 (20.7)	162 (8.4)	26 (15-99)
Risperidone	883 (13.9)	538 (8.5)	27 (19-46)
Olanzapine	265(13.9)	187 (9.8)	40 (21-312)
Quetiapine	545 (11.8)	378 (8.2)	50 (30-150)
Antidepressant	2472 (8.3)	2367 (8.0)	166 (107-362)
Valproic Acid	110 (12.2)	65 (7.2)	NS

Table 29: Mortality during 180 day observation of patients with dementia starting treatment (from 148)

They also compared mortality in patients taking different doses of the atypical antipsychotics and found that those taking more than 150mg equivalents of chlorpromazine (>4mg of olanzapine, >100mg quetiapine or > 1.5mg risperidone) daily had a significantly higher risk of mortality than those taking <75mg equivalents of chlorpromazine (ARI 3.5%, NNH = 29).[147] A more recent retrospective cohort study supports the contention that lower doses are associated with a lower risk of mortality.[149]

These rates of mortality are significantly higher than previously reported and the risk: benefit balance of their use in this indication continues to shift.

Increased Risk of Strokes

The evidence regarding increased stroke risk associated with the use of atypical antipsychotic drugs is conflicting. While several studies have reported such a link,[117 , 150,151,152], others have not. [153, 154,155]

A Cochrane review of five studies of risperidone use in dementia patients found a rate of stroke of 37/1175 (3.1%) for risperidone in 13 weeks of treatment compared to 8/779 (1%) for placebo. (OR 3.64 [95%CI 1.72-7.69] : ARI 2.1% NNH 47).[156]

Mittal et al. also reviewed the evidence relating to antipsychotic associated cerebrovascular events and mortality risk.[145] They concluded that the risk of cardiovascular events was 1.3-2 times higher in patients treated with antipsychotics. No one drug was found to safer then others in terms of the cerebrovascular risk. They also concluded that higher doses, older age of patient, presence of vascular dementia and presence of atrial fibrillation all increased the risk of strokes.[145]

The Therapeutic Goods Administration in Australia recently limited the indication for risperidone in dementia patients and restricted its use to short term management. The updated dementia-related indication for risperidone is:

- *treatment (up to 12 weeks) of psychotic symptoms, or persistent agitation or aggression unresponsive to non-pharmacological approaches in patients with moderate to severe dementia* ***of the Alzheimer type****.*

This change was based on the increased risk of strokes being more prominent in patents with vascular or mixed dementia, compared to Alzheimer's type dementia. The odds ratio for any cerebrovascular adverse event in patients with vascular or mixed dementia taking risperidone was 5.26 (95% confidence interval [CI] 1.18-48.11). The comparative odds ratio for Alzheimer's dementia patients was 2.23 (95% CI 0.85-6.88).[157]

Increased Risk of Falls

Antipsychotics are associated with an increased risk of falls. Multiple meta-analyses of the impact of drugs on falls found increased relative risk of falls associated with antipsychotic/neuroleptic use. These were reviewed recently and an overall increase in risk of at least one fall during the reported trial periods (often 12 weeks or less) was between 25-79%. [158,159,160,161,162]

A number of reviews and studies have indicated that cessation of antipsychotic agents is associated with a reduction in risk of falls.[163,164]

Recommended Prescribing Practice for Antipsychotics

Taken together, the modest efficacy and the high risk of adverse effects of antipsychotics for behaviours in dementia patients indicate a poor risk to benefit ratio (see Figure 16)

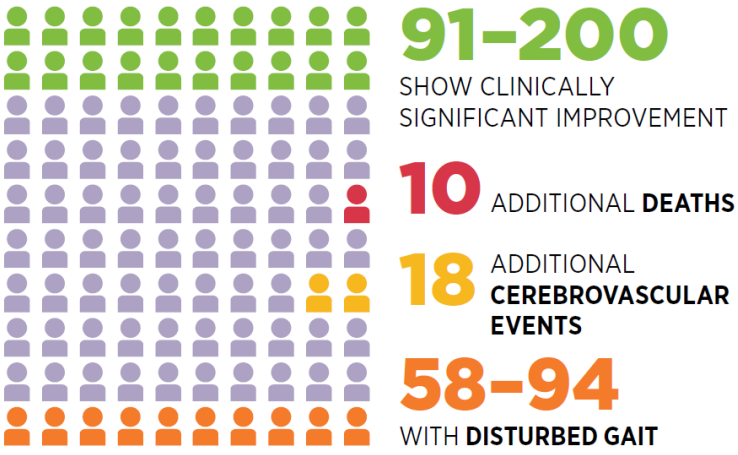


Figure 16: Outcomes for 1000 people treated with antipsychotics for BPSD (from 19)

All guidelines agree on the use of non-pharmacological measures before resorting to pharmacological treatment. Part of this includes determining if there are specific organic causes for the behaviours. The recommendations from the Royal Australian and New Zealand College of Psychiatrists have been summarised in algorithm form in Figure 17.

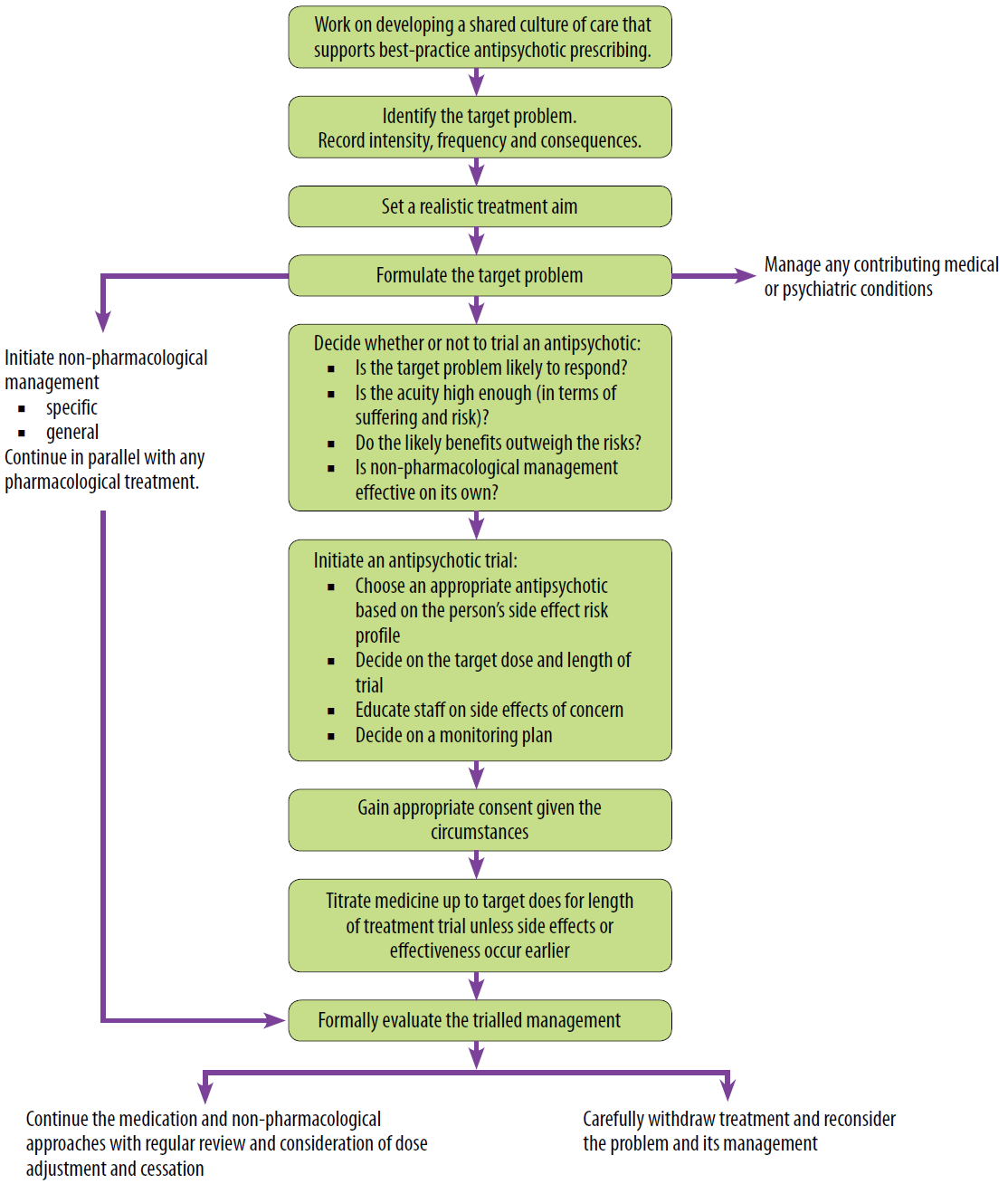
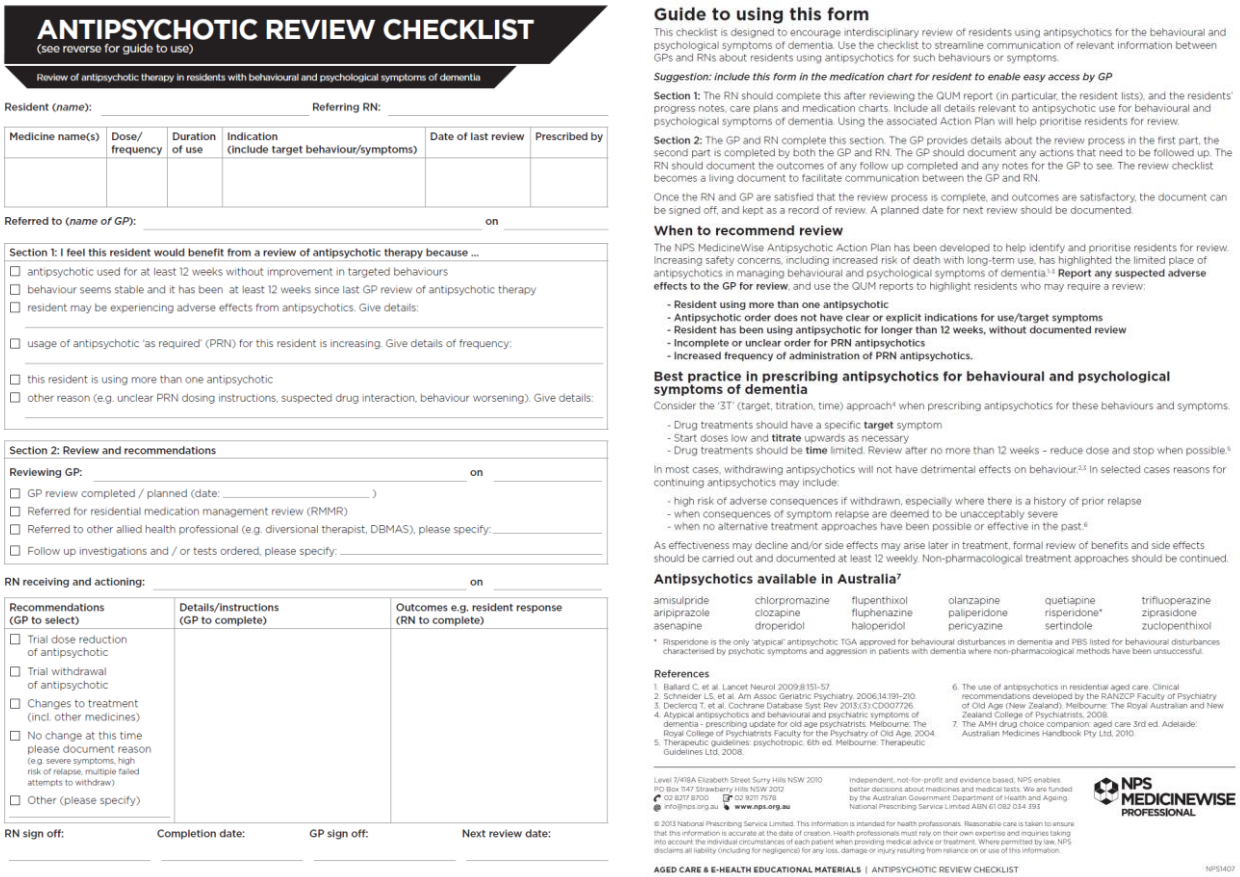


Figure 17: Algorithm for Use of Antipsychotics in Patients with Dementia (From 126,127,128)

Ongoing review of antipsychotic use is a feature of this and other treatment algorithms. The National Prescribing Service provides a detailed Antipsychotic review checklist that can be used for this purpose (see Figure 18).



ANTIPSYCHOTIC REVIEW CHECKLIST

(see reverse for guide to use)

Review of antipsychotic therapy in residents with behavioural and psychological symptoms of dementia

Resident (*name*): _____ **Referring RN:** _____

Medicine name(s)	Dose/ frequency	Duration of use	Indication (include target behaviour/symptoms)	Date of last review	Prescribed by

Referred to (*name of GP*): _____ **on** _____

Section 1: I feel this resident would benefit from a review of antipsychotic therapy because ...

- ☐ antipsychotic used for at least 12 weeks without improvement in targeted behaviours
- ☐ behaviour seems stable and it has been at least 12 weeks since last GP review of antipsychotic therapy
- ☐ resident may be experiencing adverse effects from antipsychotics. Give details:
- ☐ usage of antipsychotic 'as required' (PRN) for this resident is increasing. Give details of frequency:
- ☐ this resident is using more than one antipsychotic
- ☐ other reason (e.g. unclear PRN dosing instructions, suspected drug interaction, behaviour worsening). Give details:

Section 2: Review and recommendations

Reviewing GP: _____ **on** _____

- ☐ GP review completed / planned (date: _____)
- ☐ Referred for residential medication management review (RMMR)
- ☐ Referred to other allied health professional (e.g. diversional therapist, DBMAS), please specify: _____
- ☐ Follow up investigations and / or tests ordered, please specify: _____

RN receiving and actioning: _____ **on** _____

Recommendations (GP to select)	Details/instructions (GP to complete)	Outcomes e.g. resident response (RN to complete)
☐ Trial dose reduction of antipsychotic		
☐ Trial withdrawal of antipsychotic		
☐ Changes to treatment (incl. other medicines)		
☐ No change at this time please document reason (e.g. severe symptoms, high risk of relapse, multiple failed attempts to withdraw)		
☐ Other (please specify)		

RN sign off: _____ **Completion date:** _____ **GP sign off:** _____ **Next review date:** _____

Guide to using this form

This checklist is designed to encourage interdisciplinary review of residents using antipsychotics for the behavioural and psychological symptoms of dementia. Use the checklist to streamline communication of relevant information between GPs and RNs about residents using antipsychotics for such behaviours or symptoms.

Suggestion: include this form in the medication chart for resident to enable easy access by GP

Section 1: The RN should complete this after reviewing the QUM report (in particular, the resident lists), and the residents' progress notes, care plans and medication charts. Include all details relevant to antipsychotic use for behavioural and psychological symptoms of dementia. Using the associated Action Plan will help prioritise residents for review.

Section 2: The GP and RN complete this section. The GP provides details about the review process in the first part, the second part is completed by both the GP and RN. The GP should document any actions that need to be followed up. The RN should document the outcomes of any follow up completed and any notes for the GP to see. The review checklist becomes a living document to facilitate communication between the GP and RN.

Once the RN and GP are satisfied that the review process is complete, and outcomes are satisfactory, the document can be signed off, and kept as a record of review. A planned date for next review should be documented.

When to recommend review

The NPS MedicineWise Antipsychotic Action Plan has been developed to help identify and prioritise residents for review. Increasing safety concerns, including increased risk of death with long-term use, has highlighted the limited place of antipsychotics in managing behavioural and psychological symptoms of dementia.[1-3] **Report any suspected adverse effects to the GP for review**, and use the QUM reports to highlight residents who may require a review:

- **Resident using more than one antipsychotic**
- **Antipsychotic order does not have clear or explicit indications for use/target symptoms**
- **Resident has been using antipsychotic for longer than 12 weeks, without documented review**
- **Incomplete or unclear order for PRN antipsychotics**
- **Increased frequency of administration of PRN antipsychotics.**

Best practice in prescribing antipsychotics for behavioural and psychological symptoms of dementia

Consider the '3T' (target, titration, time) approach[4] when prescribing antipsychotics for these behaviours and symptoms.

- Drug treatments should have a specific **target** symptom
- Start doses low and **titrate** upwards as necessary
- Drug treatments should be **time** limited. Review after no more than 12 weeks – reduce dose and stop when possible.[5]

In most cases, withdrawing antipsychotics will not have detrimental effects on behaviour.[2,3] In selected cases reasons for continuing antipsychotics may include:

- high risk of adverse consequences if withdrawn, especially where there is a history of prior relapse
- when consequences of symptom relapse are deemed to be unacceptably severe
- when no alternative treatment approaches have been possible or effective in the past.[6]

As effectiveness may decline and/or side effects may arise later in treatment, formal review of benefits and side effects should be carried out and documented at least 12 weekly. Non-pharmacological treatment approaches should be continued.

Antipsychotics available in Australia[7]

amisulpride	chlorpromazine	flupenthixol	olanzapine	quetiapine	trifluoperazine
aripiprazole	clozapine	fluphenazine	paliperidone	risperidone*	ziprasidone
asenapine	droperidol	haloperidol	pericyazine	sertindole	zuclopenthixol

* Risperidone is the only 'atypical' antipsychotic TGA approved for behavioural disturbances in dementia and PBS listed for behavioural disturbances characterised by psychotic symptoms and aggression in patients with dementia where non-pharmacological methods have been unsuccessful.

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Figure 18: NPS Antipsychotic Review Checklist (from 165)

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