Conventional and atypical antipsychotics & antidepressant (trazodone) for behavioural and psychological symptoms in people with dementia

Q3: For behavioural and psychological symptoms in people with dementia, do following drugs, when compared to placebo/comparator, produce benefits/harm in the specified outcomes?

- conventional antipsychotics

- atypical antipsychotics

- antidepressant - Trazodone

Background

Worldwide, there are estimated to be 25 million people with dementia, the majority of them in developed countries have Alzheimer's disease. However, Alzheimer's disease accounts for 60% whereas vascular dementia accounts for approximately 30% of the prevalence in low and middle income countries (LAMIC). It is a devastating illness that results in a progressive decline in cognitive ability and functional capacity, causes distress to patients, their carers, and families, and has a large societal impact. Behavioural and psychological symptoms of dementia (BPSD – sometimes referred to as the non-cognitive symptoms of dementia) include: disturbances of behaviour, most of which can be subsumed under the headings of aggression and non-aggressive agitation, and psychological symptoms, particularly visual and auditory hallucinations, persecutory delusions, delusional misidentification, depression and anxiety.

BPSD are very common with point prevalence estimates ranging between 60 and 80%, and cumulative risk of 90% across the course of the illness. People with dementia are commonly affected by multiple, and recurrent behavioural problems. BPSD make a large and independent contribution to caregiver strain and are a common precipitating factor for institutionalization.

Off-label prescribing of antipsychotic drugs has been commonly employed to treat symptoms of aggression, agitation and psychosis in patients with dementia; in most countries, few or no treatments have been given regulatory approval. Atypical antipsychotic drugs (principally risperidone, olanzapine, quetiapine and aripiprazole) have to a large extent superseded the prescription of conventional (first generation) antipsychotic drugs such as haloperidol and thioridazine.

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Given the extent of the concern regarding the efficacy and safety of antipsychotic medications for the treatment of BPSD, it seems very unlikely that any more evidence from randomized placebo-controlled trials will become available to guide policy and practice. It seems likely, at least for the time being, that off-label prescribing of these agents to older people with dementia will continue. This is therefore an opportune time to reappraise the entirety of the evidence pertaining to the balance of benefits and risks associated with the use of these medications.

There is clearly a need for safer and more effective remedies, and non-antipsychotic drugs, such as trazodone, carbamazepine, valproate, chloral hydrate, and serotonin re-uptake inhibitor (SSRI) antidepressants have all been advocated. There is little empirical evidence published on the effectiveness of these agents for treating challenging behaviours in elderly people with dementia. Although published evidence is inconclusive, physicians have been using trazodone.

Population/Intervention(s)/Comparison/Outcome(s) (PICO)

Population: Individuals with dementias (cause not specified), Alzheimer's disease, vascular dementia

Interventions: Conventional (haloperidol, chlorpromazine and thioridazine),

Atypical antipsychotic drugs (risperidone, aripiprazole, quetiapine and olanzapine)

Antidepressant (trazodone)

Comparison: Placebo

Outcomes:

CONVENTIONAL ANTIPSYCHOTICS

Behavioural symptom change

Agitation

Aggression

Psychosis

Caregiver burden

Functional Status (activities of daily living)

Adverse effects (Extrapyramidal symptoms)

Improving "anxious mood" symptom (thioridazine)

ATYPICAL ANTIPSYCHOTICS

Behavioural outcome

Improving psychosis

Mortality

Falls/fractures

Cerebrovascular adverse events

TRAZODONE

Clinical Global Impression

Agitation

Cognitive functioning

Adverse events (Parkinson gait, akathesia, rigidity)

Conventional and atypical antipsychotics & antidepressant (trazodone) for behavioural and psychological symptoms in people with dementia

List of the systematic reviews identified by the search process

INCLUDED IN GRADE TABLES OR FOOTNOTES

CONVENTIONAL ANTIPSYCHOTICS

Haloperidol

Lonergan E, Luxenberg J, Colford JM (2002). Haloperidol for agitation in dementia. *Cochrane Database of Systematic Reviews,* (2):CD002852.

Thioridazine

Kirchner V, Kelly CA, Harvey RJ (2001). Thioridazine for dementia (Review). *Cochrane Database of Systematic Reviews,* (3):CD000464.

ATYPICAL ANTIPSYCHOTICS

Ballard C, Waite J (2006). The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. *Cochrane Database of Systematic Reviews,* (1):CD003476.

Schneider LS, Dagerman K, Insel PS (2006). Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. *American Journal of Geriatric Psychiatry,* 14:191-210.

Ballard C, Howard R (2006). Neuroleptic drugs in dementia: benefits and harm. *Nature* Reviews *Neuroscience,* 7:492-500.

Prince M, Castro-Costa E, Banerjee S. A systematic review of the evidence on the efficacy and harm associated with the use of conventional and atypical antipsychotics for the treatment of behavioural disturbance and psychosis in dementia (unpublished 2009).

TRAZODONE

Martinon-Torres G, Fioravanti M, Grimley Evans J (2004). Trazodone for Agitation in dementia. *Cochrane Database of Systematic Reviews,* 3:CD004990 (last assessed as up to date April 2008).

EXCLUDED FROM GRADE TABLES AND FOOTNOTES (please refer to PICO table)

Conventional and atypical antipsychotics & antidepressant (trazodone) for behavioural and psychological symptoms in people with dementia

Ballard C, Waite J (2006). The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. *Cochrane Database of Systematic Reviews,* (1):CD003476.

Schneider LS, Dagerman K, Insel PS (2006). Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. *American Journal of Geriatric Psychiatry,* 14(3):191-210.

Ballard C, Howard R (2006). Neuroleptic drugs in dementia: benefits and harm. *Nature* Reviews *Neuroscience,* 7(6):492-500.

PICO table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Haloperidol vs. placebo	Agitation Aggression Psychosis Caregiver burden Functional Status (activities of daily living) Adverse effects (extrapyramidal symptoms)	Lonergan E, Luxenberg J, Colford JM (2002). Haloperidol for agitation in dementia. *Cochrane Database of Systematic Reviews,* (2):CD002852.	This systematic review is the latest review of the area.
2	Thioridazine vs. placebo	Improving psychosis Improving depressive symptoms Improving anxiety symptoms Adverse effects	Kirchner V, Kelly CA, Harvey RJ (2001). Thioridazine for dementia. *Cochrane Database of Systematic Reviews,* (3):CD000464.	This systematic review is the latest review of the area.
3	Atypical antiphychotics vs. placebo	Psychosis Mortality Falls/Fractures Cerebrovascular adverse events	Prince M, Castro-Costa E, Banerjee S. A systematic review of the evidence on the efficacy and harm associated with the use of conventional and atypical antipsychotics for the treatment of	This systematic review considered the evidence for both conventional and atypical antipsychotics vs. placebo; latest review. The unpublished review was

			behavioural disturbance and psychosis in dementia (unpublished, 2009)	procured from the authors.
4	Trazodone vs. placebo	Clinical Global Impression Agitation Cognitive functioning Adverse event(Parkinson gait, akathesia, rigidity)	Martinon-Torres G, Fioravanti M, Grimley Evans J (2004). Trazodone for Agitation in dementia. *Cochrane Database of Systematic Reviews,* (3):CD004990 (last assessed as up to date April 2008).	Latest review on the topic

Narrative description of the studies that went into the analysis

Haloperidol

The review carried out by Lonergan et al, 2002 included five trials. Three studies were multicentre; two studies were from Europe; three studies were from the United States, three studies involved outpatients; two studies involved institutionalized patients. The average age of participants ranged between 72.1 years and 81.5 years; women made up 56.3% to 66.6% of the patients studied. Identification of dementia: all studies used one or more standard methods to diagnose dementia, including Alzheimer's dementia. Three studies were limited to Alzheimer's dementia, and two studies included other forms of dementia as well. Characterization of agitation and outcome measures: three studies used the Cohen-Mansfield Agitation Inventory (CMAI) to assess agitation and response to therapy; two studies used the Multidimensional Observation Scale for Elderly Subjects (MOSES); two studies used Brief Psychiatry Rating Scale (BPRS) and one study used the Agitated Behaviour Inventory for Dementia (ABID). Haloperidol dosage varied across the studies from 0.25mg/day to 6.0mg/day.

Thioridazine

The review carried out by Kirchner et al, 2001 found twelve trials. Four of these had suitable designs but the information reported was too brief to allow analysis. The most common reason for excluding trials was because of an open design. The eight trials that were analysed were similar in design. They were all double-blind, randomized, controlled trials of 3 to 8 weeks duration. Sample size ranged from 30 to 610 participants. Six trials not specify the type of dementia, one specified Alzheimer's Disease and one Vascular dementia. Three trials compared thioridazine with diazepam and one of these had a placebo group. Of the

remaining trials one compared thioridazine with loxapine and placebo, one with loxapine, one with zuclopentixol, one with etoperidone and one with chlormetiazole . The use of different controls constrained the pooling of results. In comparing thioridazine to diazepam and thioridazine to loxapine some items could be pooled. Mostly data were inadequately reported making pooled analyses impossible. We show only the comparisons of thioridazine with placebo.

Chlorpromazine

Studies have shown that older adults with dementia who take antipsychotics (medications for mental illness) such as chlorpromazine have an increased chance of death during treatment. Chlorpromazine is not approved by the Food and Drug Administration (FDA) for the treatment of behaviour problems in older adults with dementia. FDA in 2008 notified healthcare professionals that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis.

Atypical antipsychotics

The review carried out by Prince et al, 2009 (unpublished) included seventeen trials. For the purposes of its updated meta-analytical review, it focused mainly on the Schneider meta-analytical comparisons (Schneider et al, 2006), which were then extended to include new data from the CATIE-AD trial (two trials). All meta-analyses of individualized outcomes were re-run to generate standardized mean differences, facilitating comparison between drugs and across outcomes, The proportion responding in drug and placebo groups for dichotomized efficacy outcomes were also summarized with absolute risk differences, relative risks rather than odds ratios (which tend to overestimate the relative risk), and numbers needed to treat/ harm with 95% confidence intervals.

Trazodone

The review carried out by Martinon-Torres et al, 2004 included only two studies comprising 104 participants with dementia. The trials differed in design: one a parallel-group study of patients with Alzheimer's disease and another a cross-over study of patients with front temporal dementia with an-open label follow-up trial if three years. The results from this extension study have not been used in the analysis. It was not possible to pool the data. The studies were respectively of 16 and six weeks duration, using trazodone from 50 to 300mg daily. Both trials examined global clinical state, behavioural disturbances and cognitive function. Compared with placebo, the use of trazodone was not associated with statistically significant benefits for behavioural manifestations as measured by various rating scales. Analysis of changes from baseline for clinical impression of change and for cognitive function did not produce statistically significant results in favour of trazodone. There is insufficient evidence to recommend the use of trazodone as a treatment for behavioural and psychological manifestations of dementia.

GRADE tables

Table 1

Haloperidol

Author(s): Castro-Costa E, Dua Tarun, Huynh N
Date: 2009-08-10
Question: Should haloperidol vs. placebo be used for BPSD?
Settings: outpatients; inpatients
Bibliography: Lonergan E, Luxenberg J, Colford JM (2002). Haloperidol for agitation in dementia. *Cochrane Database of Systematic Reviews,* (2):CD002852.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	haloperidol	placebo	Relative (95% CI)	Absolute		
Behavioural symptom change (Better indicated by lower values)												
4[1]	randomized trials	serious[2]	no serious inconsistency	serious[3,4]	no serious imprecision	none	194	175	-	SMD 0.19 lower (0.4 lower to 0.01 higher)	LOW	CRITICAL
Agitation (Better indicated by lower values)												
4[1]	randomized trials	serious[2]	no serious inconsistency	serious[3,4]	no serious imprecision	none	194	175	-	SMD 0.12 lower (0.33 lower to 0.08 higher)	LOW	CRITICAL
Aggression (Better indicated by lower values)												
3[1]	randomized trials	serious[2]	no serious inconsistency	serious[5]	no serious imprecision	none	254	235	-	SMD 0.31 lower (0.44 to 0.13 lower)	LOW	CRITICAL
CGIC(improvement)												
2[1]	randomized trials	very serious[6]	no serious inconsistency	serious[5,7]	no serious imprecision	none	80/101 (79.2%)	71/103 (68.9%)	OR 1.50 (0.88 to 2.55)	80 more per 1000 (from 28 fewer to 160 more)	VERY LOW	IMPORTANT
caregiver burden (Better indicated by lower values)												

1	randomized trials	very serious[8]	no serious inconsistency	serious[9]	serious[10]	none	34	36	-	SMD 0.81 higher (0.89 lower to 2.51 higher)	VERY LOW	CRITICAL
Functional Status (activities of daily living) (Better indicated by lower values)												
1	randomized trials	very serious[8]	no serious inconsistency	serious[9]	serious[10]	none	34	36	-	SMD 0.91 higher (0.59 lower to 2.41 higher)	VERY LOW	CRITICAL
Treatment acceptability(dropouts by endpoint)												
4	randomized trials	no serious limitations[11]	no serious inconsistency	serious[3,4]	no serious imprecision	none	73/295 (24.7%)	72/278 (25.9%)	OR 1.00 (0.68 to 1.46)	0 fewer per 1000 (from 67 fewer to 79 more)	MODERATE	CRITICAL
treatment acceptability(dropouts adverse events)												
2	randomized trials	no serious limitations[11]	no serious inconsistency	serious[5,7]	no serious imprecision	none	23/135 (17%)	10/139 (7.2%)	OR 2.52 (1.22 to 5.21)	91 more per 1000 (from 14 more to 216 more)	MODERATE	CRITICAL
Extrapyramidal symptom												
1	randomized trials	very serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	34/101 (33.7%)	18/103 (17.5%)	OR 2.34 (1.25 to 4.38)	157 more per 1000 (from 35 more to 306 more)	LOW	CRITICAL

[1] From Lonergan et al, 2002

[2] drop outs more than 30% in two study.

[3] 1 study included all dementia and 3 studies included just Alzheimer's disease.

[4] different scales used to assess behavioural symptoms in 4 trials.

[5] One study included all dementia other study included Alzheimer's disease.

[6] drop outs more than 30% in both the included studies.

[7] One study is in outpatients while the other study is in hospitalized or nursing home patients.

[8] drop out more than 30% in the study.

[9] only one study contributes to the evidence base.

[10] small sample (less than 100 participants).

[11] drop outs were not considered.

Table 2

Thioridazine

Conventional and atypical antipsychotics & antidepressant (trazodone) for behavioural and psychological symptoms in people with dementia

Author(s): Castro-Costa E, Dua T, Huynh N
Date: 2009-08-11
Question: Should thioridazine vs. placebo be used for dementia?
Settings:
Bibliography: Kirchner V, Kelly CA, Harvey RJ (2001). Thioridazine for dementia. *Cochrane Database of Systematic Reviews,* (3):CD000464.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	thioridazine	placebo	Relative (95% CI)	Absolute		
adverse effects												
1[1]	randomized trials	very serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	11/17 (64.7%)	14/17 (82.4%)	OR 0.41 (0.09 to 1.86)	167 fewer per 1000 (from 528 fewer to 73 more)	VERY LOW	CRITICAL
Clinical Global evaluation (improvement)												
1[1]	randomized trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	10/17 (58.8%)	8/17 (47.1%)	OR 1.58 (0.42 to 5.96)	114 more per 1000 (from 199 fewer to 371 more)	VERY LOW	IMPORTANT
Symptoms: agitation; depressed mood; intellect, behaviour at interview												
1[1]	randomized trials	very serious[5]	no serious inconsistency	serious[3]	no serious imprecision	none	135/183 (73.8%)	74/175 (42.3%)	OR 3.64 (2.39 to 5.54)	304 more per 1000 (from 214 more to 379 more)	VERY LOW	IMPORTANT
Symptoms: anxious mood; tension; fears; insomnia												
1[1]	randomized trials	very serious[5]	no serious inconsistency	serious[3]	no serious imprecision	none	145/183 (79.2%)	72/175 (41.1%)	OR 4.91 (3.21 to 7.5)	363 more per 1000 (from 280 more to 428 more)	VERY LOW	IMPORTANT

[1] From Analysis of Kirchner et al, 2001 .

[2] more than 30% dropouts.

[3] only one study contributes to the evidence base.

[4] sample very small (less than 50 participants).
[5] drop outs not discussed.

Table 3

Aripiprazole

Author(s): Castro-Costa E, Dua T, Huynh N
Date: 2009-08-12
Question: Should aripiprazole vs. placebo be used for treatment of behavioural disturbance and psychosis in Dementia?
Settings:
Bibliography: Prince M, Castro-Costa E, Banerjee S. A systematic review of the evidence on the efficacy and harm associated with the use of conventional and atypical antipsychotics for the treatment of behavioural disturbance and psychosis in dementia (unpublished, 2009)

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	aripiprazole	placebo	Relative (95% CI)	Absolute		
BPRStotal (Better indicated by lower values)												
3	randomized trials	no serious limitations	no serious inconsistency	serious[1,2]	no serious imprecision	none	562	324	-	SMD 0.22 lower (0.36 to 0.08 lower)	MODERATE	CRITICAL
NPI total (Better indicated by lower values)												
3[3]	randomized trials	no serious limitations	no serious inconsistency	serious[1,2]	no serious imprecision	none	588	388	-	SMD 0.17 lower (0.31 to 0.03 lower)	MODERATE	CRITICAL
Cohen-Mansfield Agitation Inventory (CMAI) total (Better indicated by lower values)												
3[3]	randomized trials	no serious limitations	no serious inconsistency	serious[1,2]	no serious imprecision	none	475	236	-	SMD 0.22 lower (0.38 to 0.06 lower)	MODERATE	
NPI Psychoses(>50% improvement)												

3[3]	randomized trials	no serious limitations	no serious inconsistency	serious[1,2]	no serious imprecision	none	285/588 (48.5%)	129/338 (38.2%)	RR 1.13 (1.01 to 1.27)	50 more per 1000 (from 4 more to 103 more)	MODERATE	IMPORTANT
Mortality												
3[3]	randomized trials	no serious limitations	no serious inconsistency	serious[1,2]	no serious imprecision[4]	none	21/603 (3.5%)	6/348 (1.7%)	RR 1.50 (0.58 to 3.86)	9 more per 1000 (from 7 fewer to 49 more)	MODERATE	IMPORTANT
Cerebro vascular event												
3[3]	randomized trials	no serious limitations	no serious inconsistency	serious[1,2]	serious[4]	none	8/596 (1.3%)	2/343 (0.6%)	RR 1.29 (0.23 to 7.06)	2 more per 1000 (from 4 fewer to 35 more)	LOW	IMPORTANT

[1] 2 studies carried out in nursing home patients and 1 study in outpatients.

[2] in 2 studies doses are 2-10 mg and in one study 2-15 mg.

[3] From analysis of Prince et al, 2009.

[4] no effect with upper confidence limit crossing a risk of 2.0.

Table 4

Olanzapine

Author(s): Castro-Costa E, Dua T, Huynh N

Date: 2009-08-12

Question: Should olanzapine vs. placebo be used for treatment of behavioural disturbance and psychosis in dementia?

Settings:

Bibliography: Prince M, Castro-Costa E, Banerjee S. A systematic review of the evidence on the efficacy and harm associated with the use of conventional and atypical antipsychotics for the treatment of behavioural disturbance and psychosis in dementia (unpublished, 2009)

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	olanzapine	placebo	Relative (95% CI)	Absolute		
BPRS incl CATIE-AD 12 weeks (Better indicated by lower values)												

3[1]	randomized trials	no serious limitations	no serious inconsistency	serious[2,3]	no serious imprecision	none	808	290	-	SMD 0.13 lower (0.27 lower to 0.01 higher)	MODERATE	CRITICAL
BPRS incl CATIE-AD last phase 1 (Better indicated by lower values)												
4[1]	randomized trials	no serious limitations	no serious inconsistency	serious[2,3]	no serious imprecision	none	865	372	-	SMD 0.08 lower (0.2 lower to 0.05 higher)	MODERATE	CRITICAL
NPI incl CATIE-AD 12 weeks (Better indicated by lower values)												
4[1]	randomized trials	no serious limitations	no serious inconsistency	serious[2,3]	no serious imprecision	none	901	313	-	SMD 0.11 lower (0.24 lower to 0.02 higher)	MODERATE	CRITICAL
NPI incl CATIE-AD last phase (Better indicated by lower values)												
4[1]	randomized trials	no serious limitations	no serious inconsistency	serious[2,3]	no serious imprecision	none	958	395	-	SMD 0.10 lower (0.23 lower to 0.03 higher)	MODERATE	CRITICAL
NPI Psychosis(> 30% improvement)												
1[1]	randomized trials	no serious limitations	no serious inconsistency	serious[2,3]	no serious imprecision	none	126/204 (61.8%)	62/94 (66%)	RR 0.94 (0.78 to 1.12)	40 fewer per 1000 (from 145 fewer to 79 more)	MODERATE	IMPORTANT
Mortality												
6[1]	randomized trials	no serious limitations	no serious inconsistency	serious[2,3]	serious[4]	none	32/1284 (2.5%)	9/620 (1.5%)	RR 1.48 (0.65 to 3.39)	7 more per 1000 (from 5 fewer to 35 more)	LOW	IMPORTANT
Falls												
2[1]	randomized trials	no serious limitations	no serious inconsistency	serious[3]	serious[4]	none	57/726 (7.9%)	13/223 (5.8%)	RR 1.44 (0.8 to 2.58)	26 more per 1000 (from 12 fewer to 92 more)	LOW	IMPORTANT
cerebro vascular event												
4	randomized trials	no serious limitations	no serious inconsistency	serious[2,3]	serious[4]	none	15/1178 (1.3%)	2/478 (0.4%)	RR 1.81 (0.52 to 6.29)	3 more per 1000 (from 2 fewer to 22 more)	LOW	IMPORTANT

[1] From analysis of Prince et al, 2009 (unpublished).

[2] 2 studies carried out in nursing home and 2 studies carried in outpatients.

[3] all four studies use different doses.
[4] no effect with upper confidence limit crossing risk of 2.

Table 5

Quetiapine

Author(s): Castro-Costa E, Dua T, Huynh N
Date: 2009-08-12
Question: Should quetiapine vs. placebo be used for the treatment of behavioural disturbance and psychosis in dementia?
Settings:
Bibliography: Prince M, Castro-Costa E, Banerjee S. A systematic review of the evidence on the efficacy and harm associated with the use of conventional and atypical antipsychotics for the treatment of behavioural disturbance and psychosis in dementia (unpublished, 2009).

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	quetiapine	placebo	Relative (95% CI)	Absolute		
BPRS incl CATIE-AD 12 weeks (Better indicated by lower values)												
2[1]	randomized trials	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	154	173	-	SMD 0.25 lower (0.47 to 0.03 lower)	MODERATE	CRITICAL
BPRS CATIE-AD incl last phase (Better indicated by lower values)												
2[1]	randomized trials	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	208	155	-	SMD 0.18 lower (0.37 lower to 0 higher)	MODERATE	CRITICAL
PANNS-EC (Better indicated by lower values)												
1[1]	randomized trials	no serious limitations	no serious inconsistency	serious[2,3]	no serious imprecision	none	241	92	-	SMD 0.19 lower (0.39 lower to 0.66 higher)	MODERATE	CRITICAL
CMAI total (Better indicated by lower values)												

1[1]	randomized trials	no serious limitations	no serious inconsistency	serious[2,3]	serious[4]	none	27	29	-	SMD 0.13 higher (0.39 lower to 66 higher)	LOW	CRITICAL
BPRS total (>30% improvement)												
1[1]	randomized trials	no serious limitations	no serious inconsistency	serious[2,3]	no serious imprecision	none	32/85 (37.6%)	27/94 (28.7%)	RR 1.31 (0.86 to 1.99)	89 more per 1000 (from 40 fewer to 284 more)	MODERATE	IMPORTANT
CGI-C(much;very much improved)												
1[1]	randomized trials	no serious limitations	no serious inconsistency	serious[2,3]	serious[5]	none	99/206 (48.1%)	26/86 (30.2%)	RR 1.59 (1.12 to 2.26)	178 more per 1000 (from 36 more to 381 more)	LOW	IMPORTANT
PANSS-EC(> 40% improved)												
1[1]	randomized trials	no serious limitations	no serious inconsistency	serious[2,3]	no serious imprecision	none	75/206 (36.4%)	24/86 (27.9%)	RR 1.30 (0.89 to 1.92)	84 more per 1000 (from 31 fewer to 257 more)	MODERATE	IMPORTANT
Mortality												
4[1]	randomized trials	no serious limitations	no serious inconsistency	serious[2]	serious[5]	none	24/485 (4.9%)	10/388 (2.6%)	RR 1.57 (0.73 to 3.36)	15 more per 1000 (from 7 fewer to 61 more)	LOW	IMPORTANT

[1] from analysis of Prince et al, 2009 (unpublished, 2009).

[2] studies with different doses.

[3] only one study contributes to evidence base.

[4] small sample (<100 participants).

[5] no effect with upper confident limit crossing a risk of 2.0.

Table 6

Risperidone

Author(s): Castro-Costa E, Dua T, Huynh N

Date: 2009-08-12

Question: Should risperidone vs. placebo be used for treatment of behavioural disturbance and psychosis in dementia?

Settings:

Bibliography: Prince M, Castro-Costa E, Banerjee S. A systematic review of the evidence on the efficacy and harm associated with the use of conventional and atypical antipsychotics for the treatment of behavioural disturbance and psychosis in dementia (unpublished, 2009).

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	risperidone	placebo	Relative (95% CI)	Absolute		
Behave-AD (Better indicated by lower values)												
4[1]	randomized trials	no serious limitations	serious[2]	serious[3]	no serious imprecision	none	921	639	-	SMD 0.19 lower (0.29 to 0.08 lower)	LOW	CRITICAL
CMAI (Better indicated by lower values)												
3[1]	randomized trials	no serious limitations	no serious inconsistency	Serious[3]	no serious imprecision	none	720	427	-	SMD 0.31 lower (0.44 to 0.19 lower)	MODERATE	CRITICAL
BPRS incl 12 weeks (Better indicated by lower values)												
2[1]	randomized trials	no serious limitations	serious[2]	Serious[3]	no serious imprecision	none	215	132	-	SMD 0.06 lower (0.28 lower to 0.17 higher)	LOW	CRITICAL
BPRS incl last phase (Better indicated by lower values)												
2	randomized trials	no serious limitations	no serious inconsistency	serious[3]	no serious imprecision	none	260	214	-	SMD 0.03 lower (0.22 lower to 0.16 higher)	MODERATE	CRITICAL
NPI incl CATIE-AD (Better indicated by lower values)												
2[1]	randomized trials	no serious limitations	serious[5]	serious[3]	no serious imprecision	none	222	138	-	SMD 0.00 higher (0.21 lower to 0.22 higher)	LOW	CRITICAL
NPI incl CATIE-AD last phase (Better indicated by lower values)												
2[1]	randomized trials	no serious limitations	very serious[6]	serious[3]	no serious imprecision	none	267	221	-	SMD 0.11 lower (0.29 lower to 0.08 higher)	VERY LOW	CRITICAL

CGI-S (Better indicated by lower values)												
3[1]	randomized trials	no serious limitations	very serious[7]	serious[3]	no serious imprecision	none	616	365	-	SMD 0.19 lower (0.32 to 0.06 lower)	VERY LOW	CRITICAL
Behave-AD total												
3[1]	randomized trials	no serious limitations	no serious inconsistency	serious[3]	no serious imprecision	none	266/574 (46.3%)	139/427 (32.6%)	RR 1.42 (1.21 to 1.67)	137 more per 1000 (from 68 more to 218 more)	MODERATE	IMPORTANT
CGI-C(much;very much improved)												
2[1]	randomized trials	no serious limitations	very serious[7]	serious[3]	no serious imprecision	none	227/351 (64.7%)	175/366 (47.8%)	RR 1.35 (1.19 to 1.54)	167 more per 1000 (from 91 more to 258 more)	VERY LOW	
NPI Psychosis (> 30% improvement)												
1[1]	randomized trials	no serious limitations	no serious inconsistency	serious[3,4]	no serious imprecision	none	125/196 (63.8%)	62/94 (66%)	RR 0 (0 to 0)	660 fewer per 1000 (from 660 fewer to 660 fewer)	MODERATE	IMPORTANT
Mortality												
6[1]	randomized trials	no serious limitations	no serious inconsistency	serious[3]	serious[8]	none	46/1260 (3.7%)	25/921 (2.7%)	RR 1.29 (0.75 to 2.21)	8 more per 1000 (from 7 fewer to 33 more)	LOW	IMPORTANT
Falls												
4[1]	randomized trials	no serious limitations	no serious inconsistency	serious[3]	no serious imprecision	none	193/1060 (18.2%)	115/665 (17.3%)	RR 1.02 (0.82 to 1.27)	3 more per 1000 (from 31 fewer to 47 more)	MODERATE	IMPORTANT
Cerebrovascular event												
7[1]	randomized trials	no serious limitations	serious[9]	serious[3]	serious[8]	none	37/1175 (3.1%)	7/779 (0.9%)	RR 3.31 (1.58 to 6.96)	21 more per 1000 (from 5 more to 54 more)	VERY LOW	IMPORTANT

[1] from analysis of Prince et al, 2009 (unpublished).

[2] heterogeneity estimate (I sq)= 70%.

[3] studies with different doses.

[4] only one study contributes to the evidence base.

[5] heterogeneity estimate (I sq)= 75.2%.

[6] heterogeneity estimate (I sq)=86.8%.

[7] heterogeneity estimate (I sq)=81.9%.
[8] no effect with upper confidence limit crossing a risk of 2.0.
[9] heterogeneity estimate (I sq)= 62.1%.

Table 7

Trazodone

Author(s): Castro-Costa E, Dua T, Huynh N
Date: 2009-08-29
Question: Should trazodone vs. placebo be used for agitation?
Settings: demented patients
Bibliography: Martinon-Torres G, Fioravanti M, Grimley Evans J (2004). Trazodone for Agitation in dementia. *Cochrane Database of Systematic Reviews,* 3:CD004990 (last assessed as up to date April 2008).

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	trazodone	placebo	Relative (95% CI)	Absolute		
Clinical Global Impression 9improvement)												
1	randomized trials	serious[1]	no serious inconsistency	serious[2]	serious	none	17/111 (15.3%)	15/108 (13.9%)	OR 1.00 (0.57 to 1.77)	0 fewer per 1000 (from 55 fewer to 83 more)	VERY LOW	CRITICAL
Agitation(ABID) (Better indicated by lower values)												
1	randomized trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	74	72	-	MD 0.81 lower (5.07 lower to 3.45 higher)	VERY LOW	CRITICAL
Agitation(CMAI) (Better indicated by lower values)												
1	randomized trials	serious[1]	no serious inconsistency	serious	serious[3]	none	37	36	-	MD 5.18 higher (2.86 lower to 13.22 higher)	VERY LOW	CRITICAL

Memory(RMBPC) (Better indicated by lower values)												
1	randomized trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	37	36	-	MD 0.11 lower (0.38 lower to 0.16 higher)		IMPORTANT
Cognitive functioning(MMSE) (Better indicated by lower values)												
1	randomized trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	37	36	-	MD 1.69 lower (3.18 to 0.2 lower)	VERY LOW	IMPORTANT
Activities daily living (Better indicated by lower values)												
1	randomized trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	74	72	-	MD 0.53 higher (0.39 lower to 1.45 higher)	VERY LOW	IMPORTANT
Parkinson gait (adverse event												
1	randomized trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	4/37 (10.8%)	3/36 (8.3%)	OR 1.33 (0.28 to 6.43)	25 more per 1000 (from 59 fewer to 286 more)	VERY LOW	CRITICAL
Akathesia(adverse event)												
1	randomized trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	1/37 (2.7%)	4/36 (11.1%)	OR 0.22 (0.02 to 2.09)	84 fewer per 1000 (from 109 fewer to 96 more)	VERY LOW	CRITICAL
Rigidity(adverse event)												
1	randomized trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	3/37 (8.1%)	5/36 (13.9%)	OR 0.55 (0.12 to 2.48)	57 fewer per 1000 (from 120 fewer to 147 more)	VERY LOW	CRITICAL

[1] dropout not reported.

[2] only one study.

[3] less than 200 participants.

Additional information that was not GRADEd

Thioridazine

In December 2000, the Committee for Safety of Medicines (CSM), UK, issued an urgent cascade fax to all GPs (Wright et al, 2004), recommending that thioridazine should be restricted to second-line treatment of schizophrenia in adults and that the balance of risks and benefits is unfavourable for its previous indications (anxiety, agitation and restlessness in the elderly, moderate to severe psychomotor retardation, violent and dangerously impulsive behaviour, mania/hypomania, and behavioural disorders and epilepsy in children). The fax recommended that treatment with thioridazine should be supervised by a consultant psychiatrist (with monitoring of the patient's electroencephalogram [ECG] and electrolytes), because of concerns that thioridazine was associated with a higher risk of life-threatening arrhythmias and sudden death.

Haloperidol

Mortality has not been reported as an outcome in randomized controlled trials of haloperidol in dementia. There is insufficient evidence from randomized controlled trials to establish an increased mortality risk associated with the use of haloperidol and other conventional antipsychotics in dementia. However, data from observational studies that either compare all older users of atypical and conventional antipsychotics, or restrict these comparisons to older people with dementia, consistently suggest a slightly higher mortality (around 30%) among users of conventional antipsychotics, similar to the mortality effect observed for atypical antipsychotics.

Atypical antipsychotics

In October 2002 the manufacturer of risperidone notified Canadian healthcare professionals that in drug-sponsored clinical trials, risperidone users had been found to have a higher rate of cerebrovascular adverse events (CVAEs) relative to those receiving placebo. In 2003, the Food and Drug Administration (FDA) and other authorities published warnings and required changes to the prescribing information for risperidone. At the beginning of 2004, the European Agency for the evaluation of Medicinal Products (EMEA) also issued public advice about an increased risk of CVAEs and mortality in elderly patients with dementia receiving olanzapine. In March 2004, the UK Medicines and Healthcare products Regulatory Agency (MHRA) informed clinicians that risperidone and olanzapine should no be used to treat behavioural and psychological symptoms of dementia because of increased risk of strokes with both drugs . Similarly, in 2005 the FDA issued warnings for aripiprazole regarding the risk of CVAEs, including stroke, in elderly patients with dementia. In April 2005 the FDA informed health professionals of the results of an independent, pooled analysis of 17 RCTs reporting a 1.7 times increased risk of all cause mortality associated with atypical antipsychotic use.

Reference List

Ballard C, Howard R (2006). Neuroleptic drugs in dementia: benefits and harm. *Nature* Reviews *Neuroscience,* 7:492-500.

Ballard C, Waite J (2006). The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. *Cochrane Database of Systematic Reviews,* (1):CD003476.

FDA (2008). Information for Healthcare Professionals: Conventional Antipsychotics. (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.htm, accessed 15 February 2002).

Kirchner V, Kelly CA, Harvey RJ (2001). Thioridazine for dementia (Review). *Cochrane Database of Systematic Reviews,* (3):CD000464.

Lonergan E, Luxenberg J, Colford JM (2002). Haloperidol for agitation in dementia. *Cochrane Database of Systematic Reviews,* (2):CD002852.

Martinon-Torres G, Fioravanti M, Grimley Evans J (2004). Trazodone for Agitation in dementia. *Cochrane Database of Systematic Reviews,* 3:CD004990 (last assessed as up to date April 2008).

Prince M, Castro-Costa E, Banerjee S. A systematic review of the evidence on the efficacy and harm associated with the use of conventional and atypical antipsychotics for the treatment of behavioural disturbance and psychosis in dementia (unpublished 2009).

Schneider LS, Dagerman K, Insel PS (2006). Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. *American Journal of Geriatric Psychiatry,* 14:191-210.

Wright NMJ et al (2004). Impact of the CSM advice on thioridazine on general practitioner prescribing behaviour in Leeds: time series analysis. *British Journal of Clinical Practice,* 54:370-3.

From evidence to recommendations

Factor	Explanation
Narrative summary of the	**Haloperidol**

evidence base	Behavioural symptoms change	4 studies, SMD -0.19(-0.40 to 0.01, no difference)
	Agitation	4 studies, SMD -0.12(-0.33 to 0.08, no difference)
	Aggression	3 studies, SMD -0.31(-0.44 to -0.13 favouring active treatment)
	Improvement Psychosis	2 studies, OR 1.50(-0.88 to 2.55, no difference)
	Caregiver burden	1 study, SMD 0.81(-0.89 to 2.51 no difference)
	Functional status (activities of daily living)	1 study, SMD 0.91(-0.59 to 2.41 no difference)
	Treatment acceptability (dropouts by endpoint)	4 studies, OR 1.00(-0.68 to 1.46 no difference)
	Treatment acceptability (dropouts by adverse events)	2 studies, OR 2.52(1.22 to 4.38 favouring active treatment)
	Extrapyramidal symptoms	1 study, OR 2.34(1.25 to 4.38 favouring active treatment)
Summary of the quality of evidence	Behavioural symptoms change	LOW
	Agitation	LOW
	Aggression	LOW
	Improvement Psychosis	VERY LOW
	Caregiver burden	VERY LOW
	Functional status (activities of daily living)	VERY LOW

	Treatment acceptability (dropouts by endpoint)	MODERATE
	Treatment acceptability (dropouts by adverse events)	MODERATE
	Extrapyramidal symptom	LOW
Balance of benefits versus harms	Other than aggression, no other outcome assessing aspects of behavioural disturbance and psychosis in dementia is improved by use of haloperidol. Additionally, haloperidol could not be shown to reduce caregiver burden or to improve functional status among treated patients, compared with controls. Finally, treatment with haloperidol is associated with higher rates of adverse events such as extrapyramidal symptoms. There is insufficient evidence from randomized controlled trials to establish an increased mortality risk associated with the use of haloperidol and other conventional antipsychotics in dementia. However, data from observational studies that either compare all older users of atypical and conventional antipsychotics, or restrict these comparisons to older people with dementia, consistently suggest a slightly higher mortality (around 30%) among users of conventional antipsychotics.	
Values and preferences including any variability and human rights issues	Behavioural disturbance and psychosis associated with the cognitive decline of dementia represents a serious burden for patients and their families, particularly severe and uncontrolled agitation and aggression, where both the person with dementia, and carers may be placed at risk of harm.. However, inefficacy and adverse effects represent serious concerns regarding the use of haloperidol.	
Costs and resource use and any other relevant feasibility issues	Included in WHO Essential Medicines list	
Narrative summary of the evidence base	**Thioridazine**	
	Adverse effects	1 study, OR 0.41 (0.09 to 1.86, no difference)
	Improving psychoses (clinical global evaluation)	1 study, OR 1.58 (0.42 to 5.96, no difference)

	Improving depressive symptoms	1 study, OR 3.64 (2.39 to 5.54, favouring active treatment)
	Improving anxious symptoms(anxious mood; tension; fears; insomnia)	1 study, OR 4.91 (3.21 to 7.5, favouring active treatment)
Summary of the quality of evidence	Adverse effects	VERY LOW
	Improving psychoses (clinical global evaluation	VERY LOW
	Improving anxious symptoms(intellect, agitation; depressed mood; behaviour at interview	VERY LOW
	Adverse effects	VERY LOW
Balance of benefits versus harms	The evidence is inconclusive and so it is not possible to determine if there is a clinically significant difference between thioridazine and placebo in people with dementia. The only positive effect of thioridazine when compared to placebo is to reduce anxiety. It has high rates of adverse effects and no effect on global ratings. Serious cardiotoxicity has been detected on routine monitoring.	
Values and preferences including any variability and human rights issues	Behavioural disturbance and psychosis associated with the cognitive decline of dementia represents a serious burden for patients and their families. However, inefficacy and adverse effects represent serious concerns regarding the use of thioridazine	
Costs and resource use and any other relevant feasibility issues		

Atypical antipsychotics					
Narrative summary of the evidence base	Outcome	Aripiprazole	Olanzapine	Quetiapine	Risperidone
	Behavioural outcomes				
	BPRS total	3 studies, SMD -0.22(-0.36 to -0.08, favouring active treatment)	4 studies, SMD -0.08(-0.20 to 0.05, no difference)	2 studies, SMD-0.18(-0.37 to 0.00, no difference)	2 studies, SMD -0.03(-0.22 to 0.16, no difference)
	NPI total	3 studies, SMD -0.17(-0.31 to -0.03, favouring active treatment)	4 studies, SMD -0.10(-0.23 to 0.03, no difference)	-	2 studies, SMD -0.11(-0.29 to 0.08, no difference)
	CMAI total	3 studies, SMD -0.22(-0.38 to -0.06, favouring active treatment)	-	1 study, SMD 0.13(-0.39 to 0.66, no difference)	3 studies, SMD -0.31(-0.44 to -0.19, favouring active treatment)
	PANSS-EC	-	-	1 study, SMD -0.19(-0.43 to 0.05, no	-

				difference)	
	BEHAV-AD total	-	-	-	4 studies, SMD -0.19(-0.29 to -0.08, favouring active treatment)
	CGI-S total	-	-	-	3 studies, SMD -0.19(-0.32 to -0.06, favouring active treatment)
	Improving psychosis				
	NPI Psychosis	3 studies, RR 1.13(1.01-1.27, favouring active treatment)	1 study, RR 0.94(0.78-1.12, no difference)	-	1 study, RR 0.97(0.81-1.16, no difference)
	BPRS total	-	-	1 study, RR 1.31(0.86-1.99, no difference)	-
	CGI-C	-	-	1 study, RR 1.59(1.12-2.26, favouring active treatment	2 studies, RR 1.35(1.19-1.54, favouring active treatment)
	PANSS-EC	-	-	1 study, RR 1.30(0.89-1.92, no	-

				difference)	
	Behave-AD	-	-	-	3 studies, RR 1.42(1.21-1.67, favouring active treatment
	Adverse events				
	Mortality	3 studies, RR 1.50(0.58-3.86, no difference)	6 studies, RR 1.48(0.65-3.39, no difference)	4 studies, RR 1.57(0.73-3.36, no difference)	6 studies, RR 1.41(0.99-2.03, no difference
	Falls	-	2 studies, RR 1.44(0.80-2.58, no difference)	-	-
	Cerebrovascular event	3 studies, RR 1.29(0.23-7.06, no difference)	5 studies, RR 1.81(0.52-6.29, no difference)	-	7 studies, RR 3.31(1.58-6.96, favouring active treatment)
Summary of the quality of evidence	**Outcome**	**Aripiprazole**	**Olanzapine**	**Quetiapine**	**Risperidone**
	Behavioural outcome				
	BPRS total	MODERATE	MODERATE	MODERATE	MODERATE
	NPI total	MODERATE	MODERATE	-	LOW
	CMAI total	MODERATE	-	LOW	MODERATE
	PANSS-EC	-	-	MODERATE	-

	BEHAV-AD total	-	-	-	LOW
	CGI-S total	-	-	-	VERY LOW
	Improving psychosis				
	NPI Psychosis	MODERATE	MODERATE	-	MODERATE
	BPRS total	-	-	MODERATE	-
	CGI-C	-	-	LOW	VERY LOW
	PANSS-EC	-	-	MODERATE	-
	Behave-AD	-	-	-	MODERATE
	Adverse events				
	Mortality	MODERATE	LOW	LOW	LOW
	Falls	-	LOW	-	MODERATE
	Cerebrovascular event	LOW	LOW	-	VERY LOW
Balance of benefits versus harms	Atypical antipsychotic drugs show minimal efficacy for the treatment of behavioural symptoms in dementia. There is some evidence to support slightly greater efficacy for risperidone for the treatment of aggression, as opposed to non-aggressive agitation. Also, there is very limited evidence indeed for any efficacy of atypical antipsychotic drugs for the treatment of symptoms of psychosis. For a clinically significant degree of improvement, this has only been demonstrated for aripiprazole. Regarding adverse effects, there is suggestive evidence from randomized, placebo-controlled trial, of increased mortality associated with the use of atypical antipsychotic drugs. There is fairly consistent evidence from randomized controlled trials of risperidone and olanzapine that use of these drugs in dementia is not associated with an				

	increased incidence of falls, at least over the typical 6-12 week duration of these studies. Meta-analysed evidence from 15 randomized placebo controlled trials of atypical antipsychotics provides robust evidence for an increased risk of cerebrovascular adverse events.	
Values and preferences including any variability and human rights issues	Behavioural disturbance and psychosis associated with the cognitive decline of dementia represents a serious burden for patients and their families. However, the inefficacy and important adverse effects such as increased mortality and increased cerebrovascular events may represent serious concerns to the use of atypical antipsychotics.	
Costs and resource use and any other relevant feasibility issues	Atypical antipsychotics are associated with high acquisition costs, and treatment requires resource use and clinical and laboratory monitoring Atypical antipsychotics are not included in the WHO list of essential medicines.	
Trazodone		
Narrative summary of the evidence base	Clinical Global Impression	1 study, OR 1.00 (0.57 to 1.77, no difference)
	Agitation (ABID)	1 study, MD -0.81(-0.507 to 3.45, no difference)
	Agitation (CMAI)	1 study, MD 5.18(-2.86 to 13.22, no difference)
	Memory (RMBPC)	1 study, MD -0.11(-0.38 to 0.16, no difference)
	Cognitive functioning (MMSE)	1 study, MD -1.69(-3.18 to -0.20, favouring active treatment)
	Activities of daily living	1 study, MD 0.53(-0.39 to 1.45, no difference)
	Parkinson gait	1 study, OR 1.33(0.28 to 6.43, no difference)
	Akathesia	1 study, OR 0.22(0.02 to 2.09, no difference)

	Rigidity	1 study, OR 0.55(0.12 to 2.48, no difference)
Summary of the quality of evidence	VERY LOW for all the outcomes	
Balance of benefits versus harms	The evidence is inconclusive and so it is not possible to determine if there is a clinically significant difference between trazodone and placebo in people with dementia. There is extremely limited data available to support the use of trazodone in the treatment of behavioural disturbance and psychosis in dementia. There is no positive effect of trazodone when compared to placebo to reduce behavioural disturbance and psychosis in dementia.	
Values and preferences including any variability and human rights issues	Behavioural and psychiatric disturbances affect at least 50% of people with Alzheimer's disease and other dementias. Agitation and other challenging manifestations are common, major problems in clinical management. Aberrant behaviours contribute a great deal to caregiver burden and can make home care for patients very difficult. They are generally associated with the need for institutionalisation, rapid cognitive decline, impaired quality of life and increased healthcare costs.	
Costs and resource use and any other relevant feasibility issues	Not included in WHO Essential Medicines List	
Final recommendation(s) Thioridazine, chlorpromazine or trazodone should not be used for the treatment of behavioural and psychological symptoms of dementia. Strength of recommendation: STRONG Haloperidol and atypical antipsychotics should not be used as first line management for behavioural and psychological symptoms of dementia. Where there is clear and imminent risk of harm with severe and distressing symptoms, the short term use of haloperidol or atypical antipsychotic medications may be considered, preferably with specialist inputs. To the extent possible, informed consent and agreement should be obtained from the person and carer with regard to balance of risk and benefit.		

Conventional and atypical antipsychotics & antidepressant (trazodone) for behavioural and psychological symptoms in people with dementia

Strength of recommendation: STRONG

Limitations

The long-term consequences of antipsychotic exposure in this patient population have not been considered in the trials included in this evidence profile. Additionally, it is unclear how different antipsychotics compare in terms of efficacy and tolerability profile.

Update of the literature search – June 2012

In June 2012 the literature search for this scoping question was updated. The following systematic review was found to be relevant without changing the recommendation:

Lonergan E, Luxenberg J, Colford JM, Birks J. Haloperidol for agitation in dementia. Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No.: CD002852. DOI: 10.1002/14651858.CD002852.