Appendix D: Included Studies – adverse effects review

Table D1: Studies directly comparing two antipsychotic agents in delirium

Author	Study design	Setting	Age	Male /Female	Drug & Dose	Comparator	Mean duration
Lee 2005	Randomized controlled trial. No blinding.	Treatment of delirium in hospital	61	20/20	Amisulpiride 156 mg daily (mean)	Quetiapine 113mg daily (mean)	7 days
Miyaji 2007	Retrospective review of medical records. No blinding.	Treatment of delirium in hospital	Median 72.5	197/87	1. Oral haloperidol. Initial dose - median 0.75 (interquartile 0.75-1.5) mg. Max dose - median 1.5 (interquartile 0.75-3) mg. 2. Intravenous or intramuscular haloperidol. Initial dose - median 5 (interquartile 2.5-5) mg. Max dose - median 5 (interquartile 5-8.75) mg.	Risperidone Initial dose - median 0.5 (interquartile 0.5-1) mg. Max dose - median 1 (interquartile 0.5-2) mg.	Median 11 days.
Skrobik 2004	Quasi-randomized controlled trial. No blinding.	Treatment of delirium in the critical care setting	67	53/20	Olanzapine 5 mg (2.5mg for > 60 years)	Haloperidol initiated at 2.5- 5 mg every 8 h, with lower dose 0.5 - 1mg for age >60 years.	Mainly for 1 day only

Table D1b: Studies directly comparing two antipsychotic agents in delirium (cohort studies)

Author	Study design	Setting	Age	Male /Female	Drug & Dose	Mean duration
Gill 2005	Cohort study (retrospective and prospective elements).	Incidence of ischaemic stroke in older adults with dementia	Mean 82.6	Atypical antipsychotics 6424/11420 Typical antipsychotics 5797/9068	Risperidone (75.7%) Olanzapine (19.4%) Quetiapine (4.9%) High and low potency atypical antipsychotics prescribed	Atypical 227.2 days Typical 250.1 days
Herrmann 2004	Cohort study (retrospective).	Incidence of stroke in older adults	Mean 81.7	Typical antipsychotics 345/670 Risperidone 2159/4805 Olanzapine 1061/2360	Risperidone (61%) Olanzapine (30%) Typical antipsychotics (9%)	13,318 person years

Table D2: Studies directly comparing two antipsychotic agents in delirium

Author	Methods used for AEs	Drug	Comparator	Drug AE details			Comparator AE details
Lee 2005	"All adverse events were recorded" but method not stated	Amisulpiride n=20	Quetiapine n=20	Oversedation - 1 Acute dystonia and dyskinesia were not observed			Oversedation - 1 Acute dystonia and dyskinesia were not observed
Miyaji 2007	Two physicians checked case notes for any unfavourable sign, symptom or condition, or was listed as an adverse reaction in drug information leaflet, Events recorded irrespective of causality.	Oral haloperidol n=:95 IV/IM haloperidol: n=61	Risperidone : n=93	**Haloperidol**	**Oral**	**IV/IM**	**Control**
				Excessive sedation	19 (20%)	7 (11%)	Excessive sedation 2 (2%)
				EPS	13 (14%)	10 (16%)	EPS 2 (2%)
				Mortality during delirium	2 (2.1%)	8 (13.1%)	Mortality during delirium 3 (3.2%)
				Mortality within 1 yr after onset of delirium:	28 (29.5%)	28 (45.8%)	Mortality within 1 yr after onset of delirium: 28 (30.1%)
				Hepatic function disorder Cerebral infarction Hypothermia	1 (1%) 1 (1%) 1 (1%)		Convulsions 1 (1%)
				Incidence of any AE	30 (31.4%)	20 (32.8%)	Incidence of any AE: 6 (6.5%)
Skrobik 2004	Noted any use of antiparkinsonian medication for extrapyramidal side effects; Extrapyramidal signs were 'carefully recorded' by physician using 2 scales	Olanzapine n=45	Haloperidol n=28	Vital signs, and liver function tests were no different between groups. Patients on olanzapine had no extrapyramidal manifestations.			For haloperidol, 6 patients noted to have low scores on extrapyramidal symptom testing (1 for the Ross Chouinard, 1-4 for the Simpson-Angus scale).
				No patient in either group received prophylactic or therapeutic antiparkinsonian therapy.			

Gill 2005	Patients were observed until they were admitted to hospital with ischaemic stroke, stopped taking their antipsychotic, died or the study ended	Atypical n=17845	Typical n=14865	Incidence of ischaemic stroke	Incidence of ischaemic stroke
Herrmann 2004	Patients were observed until they were admitted to hospital for stroke, exposure to a medication from another study group, discontinuation of the drug, death or the end of the observation period	Typical n=1015	Risperidone n=6964 Olanzapine n=3421	Incidence of stroke	Incidence of stroke

Table D3: Study comparing all antipsychotics (typical and atypical) against control

Author	Study design	Setting	Age	Male /Female	Drug & Dose 1	Mean duration
Douglas 2008	Self-controlled case-series	Patients from the General Practice Research Database	Median age to first exposure to any antipsychotic drug 80	not reported	Atypical antipsychotics: Risperidone (81%) Olanzapine (18%) Quetiapine (4%) Amisulpride (4%) Typical antipsychotics: Phenothiazine (81%) Butyrophenone (20%) Thioxanthine (12%) Sulpride (3%)	Median duration of antipsychotic exposure 0.37 years (IQR 0.10 to 1.23)

Author	Methods used for AEs	Drug	Drug AE details	Comparator AE details
Douglas 2008	Intraperson comparisons in a population of individuals who have both the outcome (stoke) and exposure (antipsychotic)	Atypical antipsychotics Typical antipsychotics	Incidence of stroke	Incidence of stroke

Table D4: Studies comparing haloperidol against control in delirium

Author	Study design	Setting	Age	Male /Female	Drug & Dose 1	Comparator	Mean duration
Kalisvaart 2005	Randomized, placebo-controlled, double-blind trial	Prevention of delirium in patients having hip surgery	79	40/172	Haloperidol 1.5mg daily	Placebo	1-6 days (range)
Kaneko 1999	Randomized controlled trial. No blinding.	Prevention of delirium after GI surgery	72	24/14	Haloperidol 5 mg intravenous	Saline	5 days

Table D5: Studies comparing haloperidol against control in delirium

Author	Methods used for AEs	Drug	Comparator	Drug AE details	Comparator AE details
Kalisvaart 2005	Daily examination by the treating surgeons, spontaneous reports from the patients, and specific assessments; the Barnes Akathisia Scale and ECG, Daily BP, and assessment for sedation and extrapyramidal signs.	Haloperidol n=212	Placebo 218	Withdrawals due to AE: 3	Withdrawals due to AE: 8
				No drug-related side effects were seen during the study period. Values on the Barnes Akathisia Scale were 0 for all the patients in both groups. There was no sedation reported,	
Kaneko 1999	Frequent reassessment of the patient's mental state and careful monitoring for side effects.	Haloperidol n=40	Saline n=40	Extrapyramidal side effects not noted with intervention; however, one patient who was administered haloperidol developed transient tachycardia. No other complication	

Table D6: Studies comparing atypical antipsychotics against control in delirium

Author	Study design	Setting	Age	Male /Female	Drug & Dose	Comparator	Mean duration
Breitbart 2002	Open trial	Treatment of delirium in hospitalized cancer patients	mean 60.6, range 19 - 89	40/39	Olanzapine. Mean starting dose 3 mg (range 2.5-10). Dose after 2-3 days (T2) mean 4.6 mg (range 2.5-15). Dose after 4-7 days (T3) mean 6.3mg (range 2.5-20)	None	4-7 days
Kim 2001	Open trial	Treatment of delirium in hospital	Mean 45.8 (SD 18.3), range 19-74	15/5	Olanzapine mean 5.9 (SD 1.5) mg/day. Initial mean 4.6 (SD 0.9) mg/day. Max mean 8.8 (SD2.2) mg/day	None	6.6 (SD 1.7) days
Pae 2004	Pilot trial, open label study	Treatment of delirium in hospital	69.1 (SD 9.8), range 48-85	13/9	Quetiapine (flexible dose). Mean daily dose 127.1 (SD 72.2) mg. Mean init. dose 37.5 (SD 12.8) mg/day. Mean max dose 177.3 (SD 121) mg/day.	None	8.5 (SD 4.5) days
Parellada 2004	Prospective multicentre observational in 5 hospitals	Treatment of delirium in hospital	67	40/24	Risperidone 2.6 mg (mean)	None	7 days
Prakanratta 2007	Randomized, double blind, placebo controlled	Prevention of delirium following cardiac surgery	61	74/52	Risperidone 1mg single dose	Placebo	Single dose

Table D7: Studies comparing atypical antipsychotics against control in delirium

Author	Methods used for AEs	Drug	Comparator	Drug AE details	Comparator AE details
Breitbart 2002	Clinical (physical) examination	Olanzapine n= 79	None	Sedation 24 (30%) - reduced dosage for 8 pts. Rash, pruritus, nausea, stomach ache, dizziness, light headedness, blurred vision, headache: 3 (3.8%) Withdrawals due to AE: 2 (2.5%) [Both patients who stopped due to AE (worsening delirium) were > 80 yrs]	
Kim 2001	Not stated	Olanzapine n=20	None	Mild sedation, dry mouth: 2	
Pae 2004	Unclear	Quetiapine n=22	None	EPS, dyskinesia, dystonia: 0 Mild sedation: 3 Withdrawals due to AE: 1 (4%). (due to sedation)	
Parellada 2004	UKU Side Effect Scale for psychotropic drugs (48 symptoms in psychiatric, neurological, autonomic and other domains). Investigator reports.	Risperidone n=64	None	Total AEs: 5 Drowsiness - 2 (3.1%) Nausea - 1 (1.6%) Acute renal failure - 1 Seizure -1	
Prakanratta 2007	Certain postoperative adverse outcomes were prespecified, but no mention of adverse effects monitoring	Risperidone n=63	Placebo n= 64	Postoperative adverse outcomes: Renal Failure - 1 (3.2%) Respiratory Failure - 1 (3.2%) Arrhythmia - 1 (9.5%) Cardiovascular instability - 3 (4.8%) Tracheal re-intubation - 0	Postoperative adverse outcomes: Renal Failure - 3 (4.8%) Respiratory Failure - 4 (6.3%) Arrhythmia - 6 (9.5%) Cardiovascular instability – 4 (6.3%) Tracheal re-intubation - 4 (6.3%)

Table D8: Study comparing cholinesterase inhibitors against control in delirium

Author	Setting	Study design	Age	Male/Female	Drug & Dose	Mean duration	Comparator
Liptzin 2005	Prevention or treatment of delirium in patients having joint replacement surgery	Randomized double blind placebo controlled	67.2	34/46	Donepezil 5mg once daily	28 days	Placebo

Table D9: Study comparing cholinesterase inhibitors against control in delirium

	Methods used for AEs	Drug	Comparator	Drug AE details	Comparator AE details
Liptzin 2005	Not stated	Donepezil n=39	Placebo n=41	No difference in the rate of discontinuation. More than 25% of subjects took less than 28 days of assigned treatment. This was apparently not due to side effects, as rates (of side effects) were equivalent between drug and placebo.	

Table D10: Study comparing ondansetron against control in delirium

Author	Study design	Setting	Age	Male /Female	Drug & Dose	Comparator	Mean duration
Bayindir 2000	Open label uncontrolled trial	Treatment of post cardiotomy delirium	51	23/15	Ondansetron 8 mg iv	None	Single dose

Table D11: Study comparing ondansetron against control in delirium

Author	Methods used for AEs	Drug	Comparator	Drug AE details	Comparator AE details
Bayindir 2000	Not stated.	Ondansetron n=35	None	No constipation, headache, extrapyramidal effects, or rise in liver enzymes were observed in this study. It is safe, effective and without apparent side effects.	

Table D12: Studies reporting on stroke adverse events

<table>
<tr><th>Reference</th><th>Study type/ Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Exposed</th><th>Unexposed</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Gill et al., (BMJ 2005)</td><td>Cohort study (retrospective and prospective elements)

Canada</td><td>Total N=32710

(17,845 atypical antipsycotics; 14,865 typical antipsychotics)</td><td>Inclusion criteria: Older adults with dementia (Ontario Health Insurance plan and ICD-9 codes 290, 331 and 797); 2 cohorts: those who were new users of any of 3 atypical antipsychotics (risperidone, olanzapine and quetiapine) and those who were new users of either high potency typical antipsychotics or low potency typical antipsychotics.

Exclusion criteria: Patients receiving non-oral antipsychotics or those with other psychotic disorders that may affect their pattern of drug use. Excluded patients taking antipsychotic drug clozapine as this was rarely used at the time of the study in Ontario. Not included cohort of non-antipsychotic users as preliminary data show several important baseline differences between patients receiving antipsychotics and those not receiving antipsychotics. Not include cohorts of patients taking other psychotropics for BPSD such as trazadone or valproate, as these are used for other indications.

<table>
<tr><th>Baseline</th><th>Atypical antipsychotics (N=17845)</th><th>Typical antispychotics (N=14865)</th></tr>
<tr><td>Mean age (years)</td><td>82.5 (7.3)</td><td>82.7 (7.4)</td></tr>
<tr><td>Men/women</td><td>36%/64%</td><td>39%/61%</td></tr>
<tr><td>Risperidone
Olanzapine
Quetiapine</td><td>75.7%
19.4%
4.9%</td><td>-
-
-</td></tr>
</table>
</td><td colspan="2">Typical vs atypical antipsychotics</td><td>Mean duration of follow-up: 227.2 (264) days for atypical group; 250.1 (335.4) for typical group.

Patients were observed until they were admitted to hospital with ischaemic stroke, stopped taking their antipsychotic, died or the study ended.</td><td>Primary outcome: admission to hospital with a most responsible diagnosis of ischaemic stroke</td><td>Grant from Department of Veterans Affairs, USA.</td></tr>
</table>

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Exposed	Unexposed	Length of follow-up	Outcome measures	Source of funding

Effect size

Outcome measure	Atypical antipsychotics (N=17845)	Typical antispychotics (N=14865)
Total population (main analysis)		
Number (%) of new admissions for ischaemic stroke	284 (1.6)	227 (1.5)
Number of events per 1000 person years	25.5	22.3
Adjusted HR*	1.01 (95%CI 0.81 to 1.26)	1.0 (reference)
Subgroup analyses		
1. History of stroke		
Number (%) of new admissions for ischaemic stroke	103 (7.7)	75 (6.3)
Number of events per 1000 person years	130.4	98.2
Adjusted HR*	0.8 (0.55 to 1.16)	1.0
2. Long-term care resident at baseline		
Number (%) of new admissions for ischaemic stroke	124 (1.5)	98 (1.3)
Number of events per 1000 person years	23.7	18.4
Adjusted HR*	1.15 (0.82 to 1.60)	1.0
3. Chronic users		
Number (%) of new admissions for ischaemic stroke	214 (1.6)	163 (1.6)
Number of events per 1000 person years	20.2	17
Adjusted HR*	0.89 (0.69 to 1.17)	1.0
4. History of AF		
Number (%) of new admissions for ischaemic stroke	52 (2.6)	34 (2.0)
Number of events per 1000 person years	48.8	38
Adjusted HR*	1.23 (95%CI 0.70 to 2.02)	1.0

*Multivariate analysis (Cox proportional hazards models) adjusted for confounders: age; gender; low income; residence in long-term care; frequency of medical contact; medical conditions such as prior stroke in past 5 years, history of AF, hypertension, diabetes, acute MI in past 3 months, congestive heart failure; number of distinct drugs; chronic use of antipsychotics (≥2 consecutive prescriptions); overall burden from comorbid disease; concomitant use of drugs that may influence the risk of stroke or recognition; year of entry to the study.

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Exposed	Unexposed	Length of follow-up	Outcome measures	Source of funding
Douglas et al (BMJ 2008)	Self-controlled case-series* UK (patients from GPRD – General Practice Research Database) *Self-controlled case-series method (intraperson comparisons in a population of individuals who have both the outcome and exposure of interest. Rate ratios compare the rate of events during exposed periods of time with the rate during all other observed time periods. This removes the potential effect of confounding characteristics that vary between individuals and risk factors for vascular disease.	Total N=6790 (n=905 atypical antipsychotic, n=6334 typical antipsychotic drug) **<u>Patients with dementia:</u> Total n=1423 (n=1208 typical antipsychotic, n=85 atypical antipsychotic drug)**	**Inclusion criteria:** all patients with a first ever incident diagnosis of stroke at least 12 months after initial registration with the database. Had to have the incident of stroke before Dec 2002 and also to have been prescribed at least 1 antipsychotic medicine before this date (this was done to eliminate possible changes in prescribing pattern as concerns of AEs in elderly arose around this time) Median age to first exposure to any antipsychotic drug was 80. Most common atypical antipsychotic drug was risperidone (n=729) Risperidone 81% - Olanzapine 18% - Quetiapine 4% - Amisulpride 4%	Typical and atypical antipsychotics versus no treatment		Median duration of antipsychotic exposure 0.37 (IQR 0.10 to 1.23) years	Association between exposure to antipsychotics and Stroke	MRC of Canada

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Exposed	Unexposed	Length of follow-up	Outcome measures	Source of funding

Effect size

Outcome measure (rate ratio – association between exposure and stroke)	Any antipsychotic (N=1423)	Typical antipsychotics (N=1208)	Atypical antipsychotics (N=85)
All patients			
Exposed vs unexposed periods	1.73 (1.60 to 1.87)	1.69 (1.55 to 1.84)	2.32 (1.73 to 3.10)
Patients with recorded dementia (n=1423)			
Exposed vs unexposed periods	3.50 (2.97 to 4.12)	3.26 (2.73 to 3.89)	5.86 (3.01 to 11.38)
Days after treatment			
1-35	4.03 (3.34 to 4.87)	3.74 (3.05 to 4.59)	5.70 (2.50 to 12.98)
36-70	3.04 (2.33 to 3.96)	2.92 (2.20 to 3.88)	4.41 (1.40 to 13.89)
71-105	2.71 (1.97 to 3.73)	2.40 (1.69 to 3.41)	3.50 (0.76 to 16.25)
106-140	2.14 (1.45 to 3.15)	2.16 (1.44 to 3.23)	2.21 (0.28 to 17.34)
141-175	1.53 (0.95 to 2.44)	1.49 (0.90 to 2.44)	2.40 (0.30 to 18.88)

<table>
<tr><th>Reference</th><th>Study type/ Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Exposed</th><th>Unexposed</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Herrmann et al, (Am J Psychiatry 2004)</td><td>Cohort study (retrospective)

Canada</td><td>Total N=11400

(1015 typical antipsycotics; 6964 risperidone; 3421 olanzapine)</td><td>Inclusion criteria: individuals ≥66 years old who were given at least 2 successive prescriptions and received enough drug for 30 days of observation. Duration of exposure was the period of continuous, exclusive use of any of the study drugs starting from the index date. Hospital admissions for stroke were identified using ICD codes (430, 431, 434, 435 and 436).

<table><tr><th>Baseline</th><th>Typical antipsychotics (N=1015)</th><th>Risperidone (N=6964)</th><th>Olanzapine (N=3421)</th></tr><tr><td>Mean age (years)</td><td>81.1 (7.8)</td><td>82.9 (7.1)</td><td>81.2 (7.5)</td></tr><tr><td>Men/women</td><td>34%/66%</td><td>31%/69%</td><td>31%/69%</td></tr></table></td><td colspan="2">Typical vs atypical antipsychotics (reference)</td><td>13,318 person years of follow-up

Follow-up ended with hospital admission for stroke, exposure to a medication from another study group, discontinuation of the drug, death or end of the observation period.</td><td>Risk of stroke</td><td>None mentioned</td></tr>
<tr><td colspan="9">Effect Size

Risk ratio for stroke:
1.1 (0.5 to 2.3) with olanzapine use
1.4 (0.7 to 2.8) with risperidone use

Relative to olanzapine, users of risperidone were not at significantly increased risk of stroke-related hospital admission: adjusted risk ratio 1.3 (0.8 to 2.2)

Multivariate analysis (Cox proportional hazards model) adjusted for hospitalisations, procedures, drug utilisation hypothesised to be associated with the risk of stroke as well as basic demographic characteristics. The number of prescription drugs dispensed in the year before the index date was included as a measure of overall comorbidity.</td></tr>
</table>