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Risk of Hospitalization for Hip Fracture and Pneumonia Associated with Antipsychotic Prescribing in the Elderly

A Self-Controlled Case-Series Analysis in an Australian Health Care Claims Database

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Abstract

Background: Antipsychotics are commonly used in the elderly to treat the behavioural symptoms of dementia. Randomized controlled trial data on the safety of antipsychotics are limited and little is known about the long-term effects of these medicines. Observational studies have investigated the risk of hip fracture and pneumonia associated with the use of antipsychotics, but varying results may be due to lack of control for unmeasured confounding.

Objective: The aim of the study was to investigate the risk of hospitalization for hip fracture and pneumonia in elderly subjects exposed to antipsychotic medication using the self-controlled case-series design to control for unmeasured confounding.

Methods: The source of data for this study was the Australian Government Department of Veterans' Affairs Health Care Claims Database. A self-controlled case-series design was used to measure the excess risk of hospitalization for hip fracture and pneumonia after antipsychotic exposure compared with no-exposure over the 4-year period from 2005 to 2008.

Results: There was a significantly increased risk of hip fracture 1 week after exposure to typical antipsychotics, and the risk remained significantly raised with >12 weeks of continuous exposure (incidence rate ratio [IRR] 2.19; 95% CI 1.62, 2.95). The risk of hip fracture was highest in the first week after initiation of atypical antipsychotics (IRR 2.17; 95% CI 1.54, 3.06). The risk then declined with longer-term treatment; however, it remained significantly raised with >12 weeks of continuous exposure (IRR 1.43; 95% CI 1.23, 1.66). The risk of hospitalization for pneumonia was raised in all post-exposure periods for both typical and atypical antipsychotics.

Conclusions: Antipsychotic use in the elderly is associated with an increased risk of hospitalization for hip fracture and pneumonia. Given the increased

risks of morbidity and mortality associated with these outcomes, practitioners should consider these additional risks when prescribing antipsychotics to treat behavioural symptoms of dementia in the elderly.

Background

Antipsychotics are frequently prescribed to the elderly to treat the behavioural symptoms of dementia. Despite their widespread use, evidence from randomized controlled trials (RCTs)[1-5] of the efficacy and safety of antipsychotics in patients with dementia has been limited to the study of atypical antipsychotics, in particular risperidone. Few clinical trials exist describing the effects of typical antipsychotics in elderly patients.

Atypical antipsychotics have been associated with an improvement in symptoms such as aggression, psychosis and agitation in patients with dementia;[6] however, these improvements were limited to patients with more severe disease and were offset by adverse effects such as extrapyramidal symptoms, somnolence and more serious adverse events including cerebrovascular events[6] and death.[7] A meta-analysis of six trials found that the most common adverse event associated with death within 30 days after starting treatment with risperidone was pneumonia.[8] Data also suggest that atypical antipsychotics are associated with falls and upper respiratory tract infections.[6]

Because of the limited long-term adverse event data from RCTs concerning atypical antipsychotics, and the lack of RCT data on typical antipsychotics, observational studies have been conducted to investigate the safety of these medicines in the elderly. Such studies have identified an increased risk of hip fracture in patients taking antipsychotics compared with non-use.[9-13] One case-control study found that the risk of hip fracture increased with increased duration of exposure,[12] while another case-control study found that the risk was highest after 6 months' continuous duration but then declined to baseline levels with longer-term exposure.[13] The association between falls or fractures and antipsychotics may be due to the sedating effects of antipsychotics[12,14] and a reduction in bone mineral density due to hyperprolactinaemia.[12,15,16] An association has also been identified in observational studies between antipsychotics and pneumonia,[17,18] with the highest risk identified in the first week of treatment.[18] Antipsychotic medicines may impair swallowing function, resulting in the development of aspiration pneumonia.[17] There may be alternative explanations, other than a medication effect, for the finding of an increased risk of hospitalization for pneumonia immediately after initiating treatment with antipsychotics. Protopathic bias[19] may account for some of the association found as infections may cause increased confusion[20] or delirium,[21] leading to the dispensing of antipsychotics. The existence of protopathic bias has been suggested in other studies investigating the association between antipsychotics and pneumonia[18] and antipsychotics and stroke.[22]

The conflicting results from observational studies concerning the risk of hip fracture and pneumonia may be due to a lack of control for unmeasured confounding. Atypical antipsychotics may be selectively prescribed in the elderly as these drugs are thought to be less sedating and less likely to cause other serious adverse effects than typical antipsychotics.[6] When the reasons for prescribing are also associated with reported adverse events of the medicines, this leads to the problem of confounding. The ability of conventional observational studies to control for such confounding may be limited, particularly when utilizing administrative claims data, as these datasets often lack information on potentially important clinical confounders such as frailty, disease severity and lifestyle factors, e.g. smoking and alcohol consumption.

We used a large administrative claims database to investigate the association between antipsychotic exposure and hospitalization for hip fracture or pneumonia using the self-controlled case-series design.[23] This design compares the risk of hospitalization in periods of exposure compared

with non-exposure within the same person. It is likely to exclude the effects of major unmeasured confounders as the within-person study design controls implicitly for confounders that do not vary over time.[23]

Objective

The aim of this study was to investigate the risk of hospitalization for hip fracture and pneumonia in elderly users of antipsychotics using the self-controlled case-series design.

Methods

The source of data for this study was the Australian Government Department of Veterans' Affairs (DVA) Health Care Claims Database. DVA clients include veterans who served in the Australian Defence Force and their spouses or dependents. This dataset includes all claims data processed by the DVA and contains information relating to medicines dispensed under the Pharmaceutical Benefits Scheme and Repatriation Pharmaceutical Benefits Scheme, hospital admissions, and medical and allied health visits. Data capture for pharmaceuticals and public and private hospital admissions is complete for the population as the costs of all medicines and services are above the concessional co-payment for veterans. The data file contains 80 million pharmacy records, 200 million medical and allied health service records, and over 6 million hospital records for a treatment population of 310 000 veterans. The DVA maintains a client file, which includes data on sex, date of birth, date of death and family status. Medicines are coded according to the WHO Anatomical Therapeutic Chemical (ATC) classification[24] and the Schedule of Pharmaceutical Benefits item codes.[25] Hospitalizations are coded according to the WHO *International Classification of Diseases, 10th revision, Australian modification* (ICD-10-AM).[26]

We used the self-controlled case-series design[23,27] to compare the rate of hospitalization for hip fracture and pneumonia in periods of exposure to antipsychotics compared with unexposed periods within the same individual. All patients with a hospitalization for a primary diagnosis of hip fracture (ICD-10-AM codes S720, S721) or pneumonia (ICD-10-AM codes J12–J18) between 1 January 2005 and 31 December 2008 were selected. Only incident cases of each hospitalization event were included. Patients were included if they were aged ≥65 years as at 1 January 2005 and had been full entitlement holders (eligible for all health services) for at least 12 months at that time. Medication records were searched for all antipsychotics dispensed during the study period. The first antipsychotic dispensed was obtained and included if no other antipsychotic had been dispensed in the previous 12 months. Typical antipsychotics included chlorpromazine, trifluoperazine, periciazine, thioridazine and haloperidol. Atypical antipsychotics included clozapine, olanzapine, quetiapine, amisulpride, risperidone and aripiprazole. Patients who were initiated on both atypical and typical antipsychotics at any time during the study period were excluded. Patients exposed to injectable forms of antipsychotics were also excluded as durations of use were unable to be determined.

Since dosage information is not available in the dataset, duration of antipsychotic use was defined as the period within which 75% of veterans returned for a repeat dispensing of the medicine. These duration periods were calculated at the individual product level and represent the estimated interval between repeat dispensings. These estimated durations were then applied to each dispensed product and patients with repeat dispensings within the estimated interval were considered as continuously exposed. The end of the exposure risk period was defined as one duration period after the last dispensing of an antipsychotic if there were no further dispensings during this time. For those patients who had at least one antipsychotic dispensed during the study period, we partitioned their exposed time into risk periods: 1 week, 2–8 weeks, 9–12 weeks and all remaining exposure time post-antipsychotic initiation (>12 weeks) [figure 1a]. We also included risk periods of 1 week, 2–4 weeks, 5–8 weeks, 9–12 weeks, 13–16 weeks and 17–20 weeks prior to initiating treatment with an antipsychotic. These pre-exposure periods were partitioned from the 'unexposed' reference period for the purpose of analysis. We

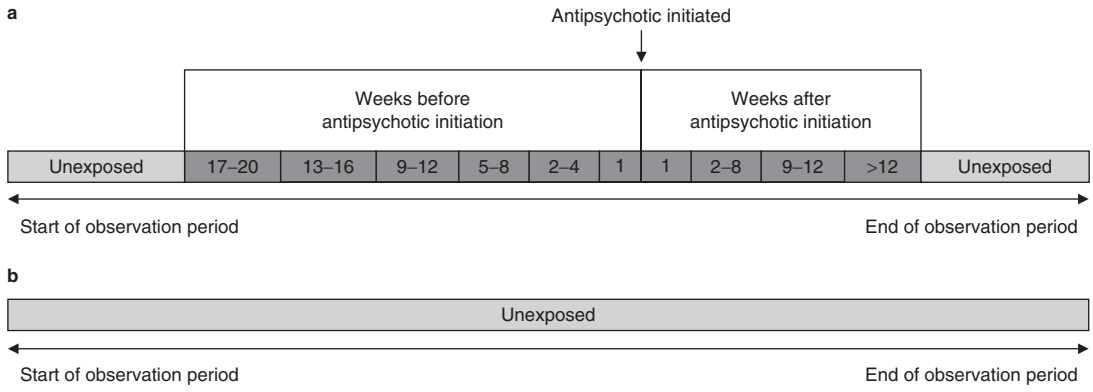

Fig. 1. (a) Representation of the self-controlled case-series analysis for exposed patients. **(b)** Representation of the self-controlled case-series analysis for unexposed patients.

included these pre-exposure risk periods to account for the possibility of an increased likelihood of an initiation of an antipsychotic after a hospitalization event. All remaining person-time was considered as 'unexposed'. The actual day of prescription was excluded from this analysis as we were unable to define the temporal association between the exposure and a hospitalization if they occurred on the same day. Patients who were hospitalized but who were not exposed to antipsychotics during the study period were also included to adjust for the increasing incidence of hospitalization with age.[23] These patients contribute information on the impact of other confounders, such as age and frailty, on the risk of the outcome.[23,27] All person-time for the unexposed group was included in the unexposed reference period (figure 1b). The incidence of outcomes in each of these exposure risk periods was compared with the incidence of outcomes in the unexposed reference period. Incidence rate ratios (IRRs) were calculated using conditional Poisson regression, adjusting for age and calendar year. All analyses were performed using SAS version 9.12 (SAS Institute, Cary, NC, USA).

To adjust for possible protopathic bias in the antipsychotic and pneumonia analysis we also performed the self-controlled case-series analysis adjusting for antibacterials commonly prescribed for respiratory tract infections: amoxicillin, amoxicillin/clavulanic acid, cefaclor, cefuroxime, erythromycin, roxithromycin, doxycycline, ciprofloxacin, oral moxifloxacin and oral gatifloxacin (ATC codes J01CA04, J01CR02, J01DC04, J01DC02, J01FA01, J01FA06, J01AA02 and J01MA02, or pharmacy item codes 08636M, 04329W and 04297E). Exposure was estimated as 14 days after the antibacterial was dispensed. We also adjusted for other medicines that may impact on the risk of fracture, including benzodiazepines[28] (ATC codes N05BA and N05CD) and oral (ATC code H02AB) and inhaled (ATC codes R03BA, R03BB, R03BC, R03BX and R03AK, excluding R03AK04) corticosteroids.[29] A time-varying term was included in the self-controlled case-series model indicating when the veteran was exposed to each of these medicines.

Results

The characteristics of the population used in the self-controlled case-series analysis are shown in table I. There were 8234 patients with at least one hospitalization for hip fracture identified in the 4-year study period. Of these, 494 patients were initiated on typical antipsychotics and 1091 were initiated on atypical antipsychotics. The median age at first hospitalization was 87 years for those initiated on typical antipsychotics and 86 years for those initiated on atypical antipsychotics. In addition, 13 324 patients with at least one hospitalization for pneumonia were identified in the 4-year study period. Of these, 807 patients were initiated on typical antipsychotics and

1107 were initiated on atypical antipsychotics. The median age at first hospitalization for pneumonia was 85 years for both those initiated on typical antipsychotics and those initiated on atypical antipsychotics.

The risk of hip fracture was significantly elevated in all post-initiation risk periods after 1 week of exposure to typical antipsychotics (table II). There was a significantly increased risk of hip fracture for up to 16 weeks prior to initiation of a typical antipsychotic, with the risk increasing steadily in the weeks leading up to first-time dispensing.

For the atypical antipsychotics, the risk of hip fracture was highest in the first week after initiation (IRR 2.17; 95% CI 1.54, 3.06), with the risk declining with longer-term treatment; however, the risk remained significantly elevated with >12 weeks of treatment (IRR 1.43; 95% CI 1.23, 1.66) [table II]. There was a significantly increased risk of hospitalization for hip fracture up to 16 weeks prior to initiation of atypical antipsychotics.

The risk of hospitalization for pneumonia was significantly increased in all post-typical and post-atypical antipsychotic exposure periods (table III). There was a significantly increased risk of hospitalization for pneumonia up to 12 weeks prior to initiation of a typical antipsychotic; however, this risk was highest in the week prior to initiation of typical antipsychotics (IRR 6.44; 95% CI 5.21, 7.95). The risk of pneumonia was elevated for up to 12 weeks prior to initiation of an atypical antipsychotic. After adjustment for the use of antibacterials, the IRR estimates were reduced marginally in the post-initiation risk periods for both typical and atypical antipsychotics, but remained significantly elevated.

Discussion

In this study we used the self-controlled case-series design to minimize possible bias due to unmeasured confounding in observational studies. We found an increased risk of hospitalization for hip fracture and pneumonia associated with antipsychotic exposure. The risk of hip fracture was increased 1 week after initiation of typical antipsychotics and persisted with longer-term exposures. The risk of hip fracture with atypical antipsychotics was highest in the first week after initiation and declined with longer-term exposures. The risk of pneumonia was significantly increased in all post-typical and post-atypical antipsychotic initiation risk periods. There was a 70–80% increased risk of pneumonia with >12 weeks of treatment with typical and atypical antipsychotics.

The results of the self-controlled case-series analyses highlight the potential for confounding by indication in observational safety studies of antipsychotics. The risk of hospitalization for both hip fracture and pneumonia was higher in the weeks leading up to initiation of typical antipsychotics compared with the same periods prior to initiating atypical antipsychotics. Our study has found that the risk of hospitalization for both hip fracture and pneumonia is highest in the week prior to typical antipsychotic initiation but not atypical antipsychotic initiation. This practice is likely to reflect the treatment of postoperative

Table I. Demographics of the study population included in the self-controlled case-series analysis

Antipsychotic exposure	No. of patients	Follow-up (y, median)	Duration of exposure (y, median)	Age at first event (y, median)	Age at first exposure (y, median)
Patients with a hospitalization for hip fracture					
Typical antipsychotics	494	3.3	0.28	87.0	86.0
Atypical antipsychotics	1 091	4.0	0.94	86.0	85.0
Unexposed	6 649	4.0	NA	85.0	NA
Patients with a hospitalization for pneumonia					
Typical antipsychotics	807	3.3	0.22	85.0	85.0
Atypical antipsychotics	1 107	3.6	0.69	85.0	85.0
Unexposed	11 410	4.0	NA	84.0	NA

NA = not applicable.

Table II. Case-series analysis for the association between first hospitalization for hip fracture and exposure to typical or atypical antipsychotics

Risk period (wk)	No. of patients	No. of hospitalizations	Person-years	IRR (95% CI)
Typical antipsychotic exposure				
Unexposed	7092	6830	22 563	1.00
Pre-typical antipsychotic initiation risk period				
17–20	408	12	34	1.52 (0.93, 2.49)
13–16	428	22	37	2.52 (1.73, 3.67)
9–12	446	16	40	1.70 (1.10, 2.62)
5–8	468	37	42	3.67 (2.71, 4.98)
2–4	489	49	33	5.92 (4.49, 7.80)
1	494	32	12	10.99 (7.94, 15.21)
Post-typical antipsychotic initiation risk period				
1	493	3	12	1.04 (0.40, 2.70)
2–8	478	39	74	2.23 (1.65, 3.02)
9–12	405	14	36	1.79 (1.12, 2.84)
>12	254	89	226	2.19 (1.62, 2.95)
Atypical antipsychotic exposure				
Unexposed	7605	7037	23 501	1.00
Pre-atypical antipsychotic initiation risk period				
17–20	881	22	76	1.16 (0.84, 1.61)
13–16	917	40	82	1.95 (1.52, 2.50)
9–12	960	66	92	2.82 (2.31, 3.46)
5–8	1014	68	108	2.46 (2.01, 3.00)
2–4	1070	56	93	2.28 (1.83, 2.84)
1	1091	26	33	2.83 (2.09, 3.85)
Post-atypical antipsychotic initiation risk period				
1	1090	20	34	2.17 (1.54, 3.06)
2–8	1070	74	219	1.27 (1.04, 1.55)
9–12	932	31	98	1.23 (0.92, 1.63)
>12	818	298	854	1.43 (1.23, 1.66)

IRR = incidence rate ratio.

delirium[30] following a hospitalization and is consistent with Australian guidelines[31] that do not recommend pharmacological treatment for delirium; however, if necessary, haloperidol may be used. The apparent selective prescribing of typical antipsychotics following a serious adverse event is likely to bias any association of the risk of hospitalization with these medicines if not adequately controlled. By partitioning the pre-initiation risk periods we have likely excluded the effects of confounding from our estimates in the post-initiation risk period. The inclusion of these separate pre-initiation risk periods is necessary in the situation where medicines are likely to be initiated in hospital. Failure to account for this would lead to an inflation of risk in the pre-initiation periods and consequently an underestimate of the incidence risk ratios in the post-initiation risk periods.[27] Other studies have used pre-exposure periods in a self-controlled case-series design, particularly when the outcome of interest is likely to lead to an increased probability of initiating treatment.[32,33] Additionally, we included an unexposed group in our analysis to adjust for the increased incidence of our outcomes, hip fracture and pneumonia, with age and the increased incidence of antipsychotic exposure with age. This inclusion is also recommended when exposure risk periods are long or indefinite,[27] which will often be the case in the analysis of medicine exposures in the elderly. Another study that investigated the risk of hospitalization for stroke associated with antipsychotics identified that when only exposed patients were included in the analysis the estimates of risk may be inflated, resulting in bias away from the null.[34] All analyses in the present study were repeated using exposed patients only (data not shown), with all estimates similar but consistently higher than those obtained when unexposed patients were included.

To account for possible protopathic bias in the antipsychotic-pneumonia association we adjusted for antibacterial dispensing in the self-controlled case-series analysis. We made this adjustment as we hypothesized that some of the increased risk of pneumonia may be due to an underlying infection, leading to delirium for which the doctors had prescribed antipsychotics. This adjustment reduced the estimate of risk marginally in the early post-initiation risk periods for both typical and atypical antipsychotics; however, the risk remained significantly elevated (table III). Protopathic bias is a logical alternative explanation for the early increased risk of pneumonia after antipsychotic initiation but is unlikely to explain the long-term increased risk. The unadjusted IRR for pneumonia in the first week after typical antipsychotic initiation was 2.07 (95% CI 1.45, 2.95) compared with the antibacterial-adjusted IRR of 1.51 (95% CI 1.07, 2.14) in the same period. After 12 weeks, the unadjusted and adjusted IRR were

similar (IRR 1.72 [95% CI 1.42, 2.08] and IRR 1.63 [95% CI 1.36, 1.96], respectively). The argument for protopathic bias with hip fracture is less clear as it is difficult to imagine a symptom that will ultimately manifest itself as a hip fracture, for which a physician is likely to prescribe antipsychotics.

One of the limitations of the present study was the reliance on hospital data only for outcome events. This approach may have missed less severe outcomes not requiring hospitalization, an omission that may have resulted in an underestimate of the true risk associated with these medicines. One of the advantages of the self-controlled case-series design is that it controls implicitly for patient-specific confounders that do not vary over time. This means that it is not necessary to adjust for variables such as sex, frailty or other risk factors for hip fracture or pneumonia that are constant over time. However, a limitation of this approach is that it is unable to adjust for changes in prescribing due to rapid changes in underlying disease severity.[27] For example, other medications that increase the risk of hip fracture or pneumonia may occur more frequently around the time of antipsychotic initiation. We adjusted

Table III. Case-series analysis for the association between first hospitalization for pneumonia and exposure to typical or atypical antipsychotics

Risk period (wk)	No. of patients	No. of hospitalizations	Person-years	IRR (95% CI)	IRR[a] (95% CI)
Typical antipsychotic exposure					
Unexposed	12 175	11 804	38 011	1.00	1.00
Pre-typical antipsychotic initiation risk period					
17–20	690	20	58	1.16 (0.87, 1.56)	1.19 (0.90, 1.57)
13–16	712	21	61	1.12 (0.85, 1.49)	1.10 (0.84, 1.44)
9–12	740	27	65	1.32 (1.02, 1.69)	1.27 (1.00, 1.62)
5–8	769	44	69	1.99 (1.62, 2.44)	1.88 (1.54, 2.29)
2–4	802	52	54	2.88 (2.38, 3.48)	2.70 (2.24, 3.25)
1	807	41	19	6.44 (5.21, 7.95)	5.57 (4.53, 6.85)
Post-typical antipsychotic initiation risk period					
1	805	13	18	2.07 (1.45, 2.95)	1.51 (1.07, 2.14)
2–8	777	66	116	1.78 (1.49, 2.12)	1.62 (1.37, 1.92)
9–12	637	28	53	1.79 (1.39, 2.30)	1.69 (1.32, 2.16)
>12	364	98	242	1.72 (1.42, 2.08)	1.63 (1.36, 1.96)
Atypical antipsychotic exposure					
Unexposed	12 383	11 835	38 309	1.00	1.00
Pre-atypical antipsychotic initiation risk period					
17–20	900	22	76	1.00 (0.76, 1.31)	1.01 (0.77, 1.31)
13–16	933	20	80	0.84 (0.63, 1.11)	0.86 (0.65, 1.13)
9–12	975	47	89	1.76 (1.45, 2.13)	1.72 (1.42, 2.07)
5–8	1 035	53	104	1.68 (1.40, 2.02)	1.65 (1.38, 1.97)
2–4	1 091	42	90	1.50 (1.22, 1.84)	1.48 (1.21, 1.81)
1	1 106	16	32	1.54 (1.12, 2.13)	1.45 (1.07, 1.98)
Post-atypical antipsychotic initiation risk period					
1	1 101	20	32	1.92 (1.44, 2.56)	1.73 (1.31, 2.29)
2–8	1 083	111	208	1.78 (1.54, 2.05)	1.70 (1.48, 1.95)
9–12	902	45	89	1.79 (1.46, 2.19)	1.67 (1.37, 2.04)
>12	752	304	722	1.81 (1.59, 2.05)	1.70 (1.51, 1.93)

a Adjusted for use of antibacterials.

IRR = incidence rate ratio.

for medicines that may also lead to confusion and an increased risk of falls or pneumonia in the elderly. This analysis showed that adjustment for benzodiazepine or corticosteroid use made little difference to our risk estimates (data not shown). Additionally, one of the assumptions of the self-controlled case-series analysis is that the occurrence of the event must not censor or affect the observation period.[23] This means that hospital events must not increase the probability of death. We are unable to determine causes of death from our data and therefore cannot estimate how many patients died as a result of pneumonia or hip fracture. Farrington and Whitaker[35] have shown that the case-series method may be robust to failure of this assumption and may result in a small negative bias; however, further work will be required to determine the extent to which our results are affected by this. Previous studies have demonstrated an increased risk of hip fracture with both typical[10,11,13] and atypical[9,10] antipsychotics, and others have demonstrated that this risk may be time-dependent.[12,13] Our study also identified that both classes of antipsychotics were associated with increased risk of hip fracture following initiation of treatment. A previous case-control study found that the risk of pneumonia was highest in the first week of treatment with antipsychotics (odds ratio 4.4; 95% CI 2.9, 7.2) but the risk returned to baseline levels after 90 days' treatment.[18] Our approach using the self-controlled case-series design found similar results for pneumonia in the weeks immediately following initiation of antipsychotics but we have identified that this risk may in fact persist with longer-term treatment with both antipsychotic classes.

Conclusions

This study found that both typical and atypical antipsychotics were associated with an increased risk of hospitalization for hip fracture and pneumonia. Given the increased risks of morbidity and mortality associated with these conditions, practitioners should consider these additional risks when prescribing antipsychotics to treat behavioural symptoms of dementia in the elderly.

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References

1. Ballard C, Fossey J, Sharp S. Antipsychotics in patients with Alzheimer's disease: what is their clinical value? Nat Clin Pract Neurol 2007; 3 (5): 248-9
2. De Deyn PP, Katz IR, Brodaty H, et al. Management of agitation, aggression, and psychosis associated with dementia: a pooled analysis including three randomized, placebo-controlled double-blind trials in nursing home residents treated with risperidone. Clin Neurol Neurosurg 2005; 107 (6): 497-508
3. Katz I, de Deyn PP, Mintzer J, et al. The efficacy and safety of risperidone in the treatment of psychosis of Alzheimer's disease and mixed dementia: a meta-analysis of 4 placebo-controlled clinical trials. Int J Geriatr Psychiatry 2007; 22 (5): 475-84
4. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry 2006; 14 (3): 191-210
5. Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med 2006; 355 (15): 1525-38
6. Ballard C, Waite J. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. Cochrane Database Syst Rev 2006; (1): CD003476
7. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005; 294 (15): 1934-43
8. Haupt M, Cruz-Jentoft A, Jeste D. Mortality in elderly dementia patients treated with risperidone. J Clin Psychopharmacol 2006; 26 (6): 566-70
9. Normand SL, Sykora K, Li P, et al. Readers guide to critical appraisal of cohort studies: 3. Analytical strategies to reduce confounding. BMJ 2005; 330 (7498): 1021-3
10. Liperoti R, Onder G, Lapane KL, et al. Conventional or atypical antipsychotics and the risk of femur fracture among elderly patients: results of a case-control study. J Clin Psychiatry 2007; 68 (6): 929-34
11. Kolanowski A, Fick D, Waller JL, et al. Outcomes of antipsychotic drug use in community-dwelling elders with dementia. Arch Psychiatr Nurs 2006; 20 (5): 217-25
12. Hugenholtz GW, Heerdink ER, van Staa TP, et al. Risk of hip/femur fractures in patients using antipsychotics. Bone 2005; 37 (6): 864-70
13. Pouwels S, van Staa TP, Egberts AC, et al. Antipsychotic use and the risk of hip/femur fracture: a population-based case-control study. Osteoporos Int 2009; 20: 1499-506
14. Cumming RG. Epidemiology of medication-related falls and fractures in the elderly. Drugs Aging 1998; 12 (1): 43-53

15. Kishimoto T, Watanabe K, Shimada N, et al. Antipsychotic-induced hyperprolactinemia inhibits the hypothalamo-pituitary-gonadal axis and reduces bone mineral density in male patients with schizophrenia. J Clin Psychiatry 2008; 69 (3): 385-91
16. Bostwick JR, Guthrie SK, Ellingrod VL. Antipsychotic-induced hyperprolactinemia. Pharmacotherapy 2009; 29 (1): 64-73
17. Wada H, Nakajoh K, Satoh-Nakagawa T, et al. Risk factors of aspiration pneumonia in Alzheimer's disease patients. Gerontology 2001; 47 (5): 271-6
18. Knol W, van Marum RJ, Jansen PA, et al. Antipsychotic drug use and risk of pneumonia in elderly people. J Am Geriatr Soc 2008; 56 (4): 661-6
19. Horwitz RI, Feinstein AR. The problem of "protopathic bias" in case-control studies. Am J Med 1980; 68 (2): 255-8
20. Byrne GJ. Pharmacological treatment of behavioural problems in dementia. Aust Prescr 2005; 28: 67-70
21. Oldenbeuving AW, de Kort PL, Jansen BP, et al. Delirium in acute stroke: a review. Int J Stroke 2007; 2 (4): 270-5
22. Kleijer BC, van Marum RJ, Egberts AC, et al. Risk of cerebrovascular events in elderly users of antipsychotics. J Psychopharmacol 2009; 23: 909-14
23. Whitaker HJ, Farrington CP, Spiessens B, et al. Tutorial in biostatistics: the self-controlled case series method. Stat Med 2006; 25 (10): 1768-97
24. World Health Organization Collaborating Centre for Drug Statistics Methodology. Anatomical therapeutic chemical code classification index with defined daily doses [online]. Available from URL: http://www.whocc.no/atcddd/ [Accessed 2011 Apr 18]
25. Australian Government Department of Health and Ageing. Schedule of pharmaceutical benefits. PBS for health professionals [online]. Available from URL: http://www.pbs.gov.au/pbs/home [Accessed 2011 May 2]
26. National Centre for Classification in Health. The international statistical classification of diseases and related health problems, 10th revision, Australian modification (ICD-10-AM). 6th ed. National Centre for Classification in Health, Faculty of Health Sciences, University of Sydney, 2005
27. Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. Stat Methods Med Res 2009; 18: 7-26
28. Wang PS, Bohn RL, Glynn RJ, et al. Hazardous benzodiazepine regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture. Am J Psychiatry 2001; 158 (6): 892-8
29. Hubbard R, Tattersfield A, Smith C, et al. Use of inhaled corticosteroids and the risk of fracture. Chest 2006; 130 (4): 1082-8
30. Robertson BD, Robertson TJ. Postoperative delirium after hip fracture. J Bone Joint Surg Am 2006; 88 (9): 2060-8
31. eTG Complete. West Melbourne (VIC): therapeutic guidelines, 2010 [online]. Available from URL: http://www.tg.org.au/index.php?sectionid=71 [Accessed 2001 May 2]
32. Gibson JE, Hubbard RB, Smith CJ, et al. Use of self-controlled analytical techniques to assess the association between use of prescription medications and the risk of motor vehicle crashes. Am J Epidemiol 2009; 169 (6): 761-8
33. Hubbard R, Lewis S, Smith C, et al. Use of nicotine replacement therapy and the risk of acute myocardial infarction, stroke, and death. Tob Control 2005; 14 (6): 416-21
34. Pratt NL, Roughead EE, Ramsay E, et al. Risk of hospitalisation for stroke associated with antipsychotic use in the elderly: self controlled case-series results. Drugs Aging. 2010; 27: 885-93
35. Farrington CP, Whitaker HJ. Semiparametric analysis of case series data. Appl Stat 2006; 55 (Pt 5): 553-94

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