

Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study

Sudeep S Gill, Paula A Rochon, Nathan Herrmann, Philip E Lee, Kathy Sykora, Nadia Gunraj, Sharon-Lise T Normand, Jerry H Gurwitz, Connie Marras, Walter P Wodchis, Muhammad Mamdani

Abstract

Objective To compare the incidence of admissions to hospital for stroke among older adults with dementia receiving atypical or typical antipsychotics.

Design Population based retrospective cohort study.

Setting Ontario, Canada.

Patients 32 710 older adults (≥ 65 years) with dementia (17 845 dispensed an atypical antipsychotic and 14 865 dispensed a typical antipsychotic).

Main outcome measures Admission to hospital with the most responsible diagnosis (single most important condition responsible for the patient's admission) of ischaemic stroke. Observation of patients until they were either admitted to hospital with ischaemic stroke, stopped taking antipsychotics, died, or the study ended.

Results After adjustment for potential confounders, participants receiving atypical antipsychotics showed no significant increase in risk of ischaemic stroke compared with those receiving typical antipsychotics (adjusted hazard ratio 1.01, 95% confidence interval 0.81 to 1.26). This finding was consistent in a series of subgroup analyses, including ones of individual atypical antipsychotic drugs (risperidone, olanzapine, and quetiapine) and selected subpopulations of the main cohorts.

Conclusion Older adults with dementia who take atypical antipsychotics have a similar risk of ischaemic stroke to those taking typical antipsychotics.

Introduction

The term behavioural and psychological symptoms of dementia—BPSD—describes the spectrum of behavioural disturbances that commonly accompany dementia, such as physical aggression and hallucinations.¹ Atypical antipsychotics are often prescribed to manage BPSD. Although such prescriptions represent off-label prescribing, this practice is widely endorsed because these drugs are among the best studied for treating BPSD.²⁻³ Concerns, however, have been raised that atypical antipsychotics may increase the risk of cerebrovascular adverse events, including stroke, among older adults with BPSD.

Since October 2002, several warnings have been issued of a possible link between use of atypical antipsychotics and the risk of cerebrovascular adverse events.⁴⁻⁹ To date, these warnings only extend to older adults receiving atypical antipsychotics for BPSD and not to patients receiving these drugs for schizophrenia or other indications. No warnings have been issued on the use of other atypical agents, such as quetiapine or aripiprazole, as few studies have been published on their use to manage BPSD.

We compared the incidence of admissions to hospitals for stroke among older adults with dementia

receiving atypical antipsychotics or typical antipsychotics.

Methods

From administrative databases in Ontario, Canada, we identified older adults (aged 65 or more) with a diagnosis of dementia and with no history of antipsychotic drug use. We used encrypted unique identifiers to link anonymous information between databases on personal details and use of health services for patients in our study. The databases included computerised pharmacy records of the Ontario Drug Benefit Database, which records prescription drugs dispensed to all Ontario residents aged 65 years or older. Records for admission to hospital for acute care were obtained from the Canadian Institute for Health Information Discharge Abstract Database, which uses ICD-9 (international classification of diseases, 9th revision) codes for diagnostic records for all hospital admissions. We obtained information on doctor billing for inpatient and outpatient services from the records of the Ontario Health Insurance Plan, and basic personal information and vital statistics for each patient from the Registered Persons Database.

Cohort

We identified two cohorts of older adults with dementia: new users of any of three atypical antipsychotics (risperidone, olanzapine, and quetiapine) and new users of high potency typical antipsychotics or low potency typical antipsychotics. Typical antipsychotics were haloperidol, fluphenazine, thiothixene, pimozide, trifluoperazine, flupenthixol, zuclopenthixol, thiopropazine, chlorpromazine, thioridazine, mesoridazine, loxapine, perphenazine, promazine, pericyazine, and chlorprothixane. We excluded patients who were receiving non-oral antipsychotics, those with psychotic disorders that might affect their pattern of drug use, and those taking the atypical antipsychotic clozapine, which was not commonly used in Ontario during our study period. We did not include a cohort of non-antipsychotic users, as preliminary data show several important baseline differences between patients receiving antipsychotics and those not receiving antipsychotics.

We enrolled patients into the cohorts between 1 April 1997 and 31 March 2002. To restrict our cohorts to new users, we looked back one year from the first date the antipsychotic was dispensed to ensure that no such drugs had been previously prescribed. We considered that exposure to the antipsychotic had stopped if no further data on a dispensed drug were

Institute for Clinical Evaluative Sciences, 2075 Bayview Avenue, Toronto, ON, Canada

Sudeep S Gill
adjunct scientist

Kathy Sykora
senior biostatistician

Nadia Gunraj
biostatistician

Muhammad Mamdani
scientist

Kunin-Lunenfeld Applied Research Unit, Baycrest Centre for Geriatric Care, Toronto
Paula A Rochon
assistant director

Division of Geriatric Psychiatry, Department of Psychiatry, Sunnybrook and Women's College Health Sciences Centre, Toronto

Nathan Herrmann
head

Morton and Gloria Shulman Movement Disorders Centre, Toronto Western Hospital, Toronto

Connie Marras
neurologist

Toronto Rehabilitation Institute, Toronto
Walter P Wodchis
scientist

Division of Geriatric Medicine, University of British Columbia, Vancouver, BC, Canada
Philip E Lee
geriatrician

Department of Health Care Policy, Harvard Medical School and Harvard School of Public Health, Boston, MA, USA

Sharon-Lise T Normand
professor of biostatistics

continued over

BMJ 2005;330:445-8



This is the abridged version of an article that was posted on bmj.com on 24 January 2005: <http://bmj.com/cgi/doi/10.1136/bmj.38330.470486.8F>

Meyers Primary
Care Institute,
University of
Massachusetts
Medical School,
Worcester, MA
Jerry H Gurwitz
professor

Correspondence to:
S S Gill, Room
1-152, Chapel
Wing, St Mary's of
the Lake Hospital,
340 Union Street,
Kingston, ON,
Canada K7L 5A2
gills@pccchealth.org

Table 1 Event rates and hazard ratios for older adults with dementia receiving atypical or typical antipsychotics

Main analysis (full cohorts)	Atypical antipsychotic cohort (n=17 845)	Typical antipsychotic cohort (n=14 865)
No (%) of new admissions for ischaemic stroke	284 (1.6)	227 (1.5)
Mean (SD) duration of follow up (days)	227.2 (264.0)	250.1 (335.4)
Crude event rate (No of events per 1000 person years)*	25.5	22.3
Unadjusted hazard ratio (95% CI)	1.06 (0.89 to 1.27)	1.00
Adjusted hazard ratio (95% CI)†	1.01 (0.81 to 1.26)	1.00

* (No of events/total No of days per 365 days)×1000.

†Adjusted for age; sex; low income status; residence in long term care; frequency of medical contact; year of entry to cohort; history of stroke in past five years; history of atrial fibrillation; hypertension; diabetes mellitus; acute myocardial infarction in past three months; congestive heart failure; number of distinct drugs; chronic use (≥2 consecutive prescriptions) of antipsychotics; and baseline use of warfarin, antiplatelet drugs, antihypertensive drugs, angiotensin converting enzyme inhibitors, lipid lowering drugs, antidiabetic drugs, and hormone replacement therapy.

recorded in the Ontario Drug Benefit Database within a period of two times the total days supplied for the initial date the drug was dispensed.

Ischaemic stroke

Our primary outcome was admission to hospital with a most responsible diagnosis of ischaemic stroke. Most responsible diagnosis refers to the single most important condition responsible for admission and is used by trained abstractors who complete data collection for the Canadian Institute for Health Information to distinguish between the main reason for admission and comorbid conditions. We were therefore able to distinguish between old strokes and new outcome events.

We focused on the outcome of stroke for several reasons: the diagnostic accuracy for transient ischaemic attacks is relatively poor in administrative databases, comparatively few patients with transient ischaemic attacks are admitted to hospital, and the risk of stroke immediately after a transient ischaemic attack is high.^{10–15}

Patients were observed until they were admitted to hospital with ischaemic stroke, stopped taking antipsychotics, died, or the study ended (31 March 2002). Patients in the cohort receiving atypical antipsychotics were censored if they switched between atypical antipsychotics, to allow us to assess hazards associated with each of the three atypical drugs under study. Patients in the cohort receiving typical antipsychotics were censored if they switched to atypical antipsychotics.

Statistical analysis

We first calculated crude incidence rates of stroke for the cohorts, using the number of events per 1000 patient years. To examine the independent effect of use of atypical antipsychotics on developing ischaemic stroke, we conducted survival analysis using Cox proportional hazards models. Covariates included factors that would influence the development or the recognition of incident ischaemic stroke: age; sex; low income status; residence in long term care; frequency of medical contact (number of physician claim days per patient per year); medical conditions such as prior stroke, atrial fibrillation, diabetes mellitus, acute myocardial infarction in the past three months, congestive heart failure; and overall burden from comorbid disease.¹⁴ As an overall measure of comorbidity, we used the number of distinct drugs dispensed in the year before entry to the cohort.¹⁵ We also controlled for the concomitant use of drugs that might influence the risk of stroke (for example, antihypertensives). Finally, given the potential for changes in patient care during our study, we controlled for year of entry to the study.

We carried out subgroup analyses on selected populations of the cohorts. This was done to examine subgroups that either were similar to patients in the trials (for example, most patients in the trials of atypical antipsychotics for managing BPSD were in long term care¹⁶) or were at high risk of stroke (for example, a history of prior stroke or atrial fibrillation).

We carried out a subgroup analysis of patients enrolled between 1 April 2000 and 31 March 2002 to address major shifts in the prescribing of atypical antipsychotics and typical antipsychotics between 1997 and 2002.

Results

We identified 32 710 older adults with dementia (17 845 dispensed atypical antipsychotics and 14 865 dispensed typical antipsychotics). The atypical antipsychotic cohort included 13 503 (75.7%) patients receiving risperidone, 3459 (19.4%) receiving olanzapine, and 883 (4.9%) receiving quetiapine. The cohorts had similar baseline characteristics (see [bmj.com](#)). Baseline characteristics were also similar for the subcohorts taking high potency typical antipsychotics (57.1%) and low potency (42.9%) typical antipsychotics (data not shown). Traditional risk factors for ischaemic stroke, such as atrial fibrillation and prior stroke, were common among older adults with dementia.

We found that the risk of ischaemic stroke in older adults with dementia receiving atypical antipsychotics was not significantly different from those receiving typical antipsychotics (unadjusted hazard ratio 1.06, 95% confidence interval 0.89 to 1.27; adjusted hazard ratio 1.01, 0.81 to 1.26; table 1).

The risk of stroke for patients receiving risperidone (adjusted hazard ratio 1.04, 0.82 to 1.31), olanzapine (0.91, 0.62 to 1.32), and quetiapine (0.78, 0.38 to 1.57) was not significantly different from that of patients receiving typical antipsychotics. Analyses on selected populations of the cohorts showed no significant differences in the development of stroke between the cohorts receiving atypical antipsychotics and those receiving typical antipsychotics (table 2). Chronic users (two or more consecutive prescriptions) of atypical antipsychotics were not at increased risk of stroke compared with chronic users of typical antipsychotics.

The risk of stroke in the subgroup of patients enrolled between 1 April 2000 and 31 March 2002 was not significantly different between those receiving atypical antipsychotics and those receiving typical antipsychotics (adjusted hazard ratio 0.98, 95% confidence interval 0.65 to 1.47).

Table 2 Event rates and hazard ratios for subgroup analyses of older adults with dementia receiving atypical or typical antipsychotics

Characteristics	Atypical antipsychotic cohort	Typical antipsychotic cohort
History of stroke	(n=1330)	(n=1189)
No (%) of new admissions for ischaemic stroke	103 (7.7)	75 (6.3)
Mean (SD) duration of follow up (days)	217.1 (251.8)	235.0 (336.2)
Crude event rate (No of events per 1000 person years)*	130.4	98.2
Unadjusted hazard ratio (95% CI)	1.18 (0.88 to 1.59)	1.00
Adjusted hazard ratio (95% CI)†	0.80 (0.55 to 1.16)	1.00
Long term care resident at baseline	(n=8485)	(n=7682)
No (%) of new admissions for ischaemic stroke	124 (1.5)	98 (1.3)
Mean (SD) duration of follow up (days)	225.7 (267.2)	253.1 (336)
Crude event rate (No of events per 1000 person years)*	23.7	18.4
Unadjusted hazard ratio (95% CI)	1.18 (0.91 to 1.54)	1.00
Adjusted hazard ratio (95% CI)†	1.15 (0.82 to 1.60)	1.00
Chronic users‡	(n=13 792)	(n=9929)
No (%) of new admissions for ischaemic stroke	214 (1.6)	163 (1.6)
Mean (SD) duration of follow up (days)	280.6 (277.7)	352.7 (367.1)
Crude event rate (No of events per 1000 person years)*	20.2	17
Unadjusted hazard ratio (95% CI)	1.11 (0.91 to 1.37)	1.00
Adjusted hazard ratio (95% CI)†	0.89 (0.69 to 1.17)	1.00
History of atrial fibrillation	(n=1992)	(n=1672)
No (%) of admissions for ischaemic stroke	52 (2.6)	34 (2.0)
Mean (SD) duration of follow up (days)	195.6 (233.1)	195.6 (288.6)
Crude event rate (No of events per 1000 person years)*	48.8	38
Unadjusted hazard ratio (95% CI)	1.23 (0.79 to 1.89)	1.00
Adjusted hazard ratio (95% CI)†	1.23 (0.70 to 2.02)	1.00

* (No of events/total No of days per 365 days)×1000.

† Adjusted for age; sex; low income status; residence in long term care; frequency of medical contact; year of entry to cohort; history of stroke in past five years; history of atrial fibrillation; hypertension; diabetes mellitus; acute myocardial infarction in past 3 months; congestive heart failure; number of distinct drugs; chronic use (≥2 consecutive prescriptions) of antipsychotics; baseline use of warfarin, antiplatelet drugs, antihypertensives, angiotensin converting enzyme inhibitors, lipid lowering drugs, antidiabetic drugs, and hormone replacement therapy. Factors not included in risk adjustment when they were focus of subgroups analysis were residence in long term care, history of stroke in past five years, history of atrial fibrillation, and chronic use of antipsychotics.

‡ ≥2 consecutive prescriptions.

Discussion

In this population based cohort, older adults with behavioural and psychological symptoms of dementia (BPSD) who received atypical antipsychotics had a similar risk of ischaemic stroke as those receiving typical antipsychotics.

The incidence rates for stroke in our study corresponded well with those reported by other investigators.¹⁷ We found higher incidence rates of stroke in those subgroups with established risk factors for stroke, such as atrial fibrillation and prior stroke, than in the main analysis. In contrast, we found no increase in risk among chronic users (two or more consecutive prescriptions) of atypical antipsychotics, suggesting the absence of an association between atypical antipsychotics and cerebrovascular events.

Several investigators found no association between use of atypical antipsychotics and cerebrovascular events.^{18–20} Our study supports these findings. In contrast, earlier clinical trials of risperidone and olanzapine found a link between use of atypical antipsychotics and cerebrovascular adverse events, including ischaemic stroke.^{6–8} It could be speculated that in these trials events other than transient ischaemic attacks and strokes were classified as “cerebrovascular adverse events.” The risk seems to develop quickly (6–12 weeks in clinical trials), and thus it seems unlikely that the risk is mediated through drug effects on risk factors such as glucose or lipid metabolism. Potential mechanisms for cerebrovascular events related to atypical antipsychotics might include orthostatic hypotension in patients with pre-existing cerebrovascular disease, which might lead to “watershed” strokes,²¹ and antipsychotic induced hyperprolactinaemia, which might promote platelet

aggregation.^{21–22} Others have reported that risperidone may inhibit platelet aggregation (through serotonin receptor antagonism) rather than promote it.²³ Some observational data have shown that antipsychotics might be associated with an increased risk of venous thromboembolic disease²⁴; arterial thrombosis such as stroke, however, shares few risk factors with venous thrombosis. In summary, a clear biological rationale has not yet been identified for an increased risk of stroke associated with use of atypical antipsychotics.

Limitations of study

Our study has several potential limitations. Firstly, our study was observational, and although the baseline differences between our cohorts were minor, we may not have adjusted adequately for such differences. Important confounders may also have been unmeasured and unrecognised. We tried to avoid confounding by indication by excluding data from the period after the first warning of cerebrovascular adverse events was issued (October 2002).⁴ Secondly, despite the potential for ascertainment bias, because some strokes may not have been captured if they did not lead to admission to hospital or if they led immediately to death, we kept our primary outcome as admission to hospital for stroke given the accuracy with which this diagnosis is captured in the data we used. Thirdly, given the limitations of the administrative data, we could not adjust for all of the important factors affecting the risk of stroke, such as smoking history and the presence and severity of hypertension.

What do these results mean for clinical practice? Clinicians managing patients with dementia who develop behavioural disturbances should initially rule out underlying medical illnesses or drugs that might predispose to

What is already known on this topic

Atypical antipsychotics are commonly used to manage behavioural and psychological symptoms of dementia (BPSD)

Evidence from clinical trials suggests an association between atypical antipsychotic use and cerebrovascular events (including stroke) among older adults with BPSD

What this study adds

Use of atypical antipsychotics by patients with dementia is not associated with a greater risk of stroke than use of typical antipsychotics

Findings were consistent for a series of subgroup analyses including ones for patients at high baseline risk of stroke

The choice between atypical and typical antipsychotic drugs to manage BPSD should not be based on concerns about the risk of stroke

delirium.²⁵ If BPSD is diagnosed, non-pharmacological harm reduction strategies should be considered such as education of family members.²⁶ If pharmacotherapy is deemed necessary, it should be tailored to the individual. Other potential risks of antipsychotics (for example, extrapyramidal symptoms) should be weighed against the benefits. A working group of psychiatrists, general practitioners, and geriatricians in the United Kingdom has developed guidelines for the management of BPSD in people with a history of stroke or transient ischaemic attack.²⁷ The US National Institute of Mental Health is currently sponsoring a 36 week study comparing three atypical antipsychotics, a selective serotonin reuptake inhibitor, and placebo to treat BPSD. Results are due in 2006.²⁸

We thank the following members of the New Emerging Team for their input: S Garfinkel, C Bell, GM Anderson, MP Hillmer, and A Bierman.

Contributors: SSG, PAR, NH, PEL, and MM conceived the study. All authors contributed to the study design. KS, NG, and SSG performed the data analysis. SSG wrote the initial draft, and all authors critically revised the manuscript. PAR and MM were overseers of the research network. SSG will act as guarantor for the paper.

Funding: SSG was supported by a Canadian Institutes of Health Research postdoctoral fellowship and the Annie Kirshenblatt memorial scholarship. PAR is supported by a Canadian Institutes of Health Research investigator award. Eli Lilly Canada part supported PEL's behavioural neurology fellowship. This work was supported by a Canadian Institutes of Health Research Chronic Disease New Emerging Team programme grant (NET 54010). The NET programme receives joint sponsorship from the Canadian Diabetes Association, the Kidney Foundation of Canada, the Heart and Stroke Foundation of Canada, and the Canadian Institutes of Health Research Institutes of Nutrition, Metabolism, and Diabetes, and Circulatory and Respiratory Health. MM was supported in part by a new investigator award through the NET programme.

Competing interests: NH has received research support and speakers' honorariums from Janssen-Ortho, Eli Lilly, Novartis, Pfizer, and Astra Zeneca, manufacturers of atypical antipsychotics. Ethical approval: This study was approved by the ethics review board of Sunnybrook and Women's College Health Sciences Centre.

- Cohen-Mansfield J, Billig N. Agitated behaviours in the elderly. I: a conceptual review. *J Am Geriatr Soc* 1998;36:7-12.
- Doody RS, Stevens JC, Beck C, Dubinsky RM, Kaye JA, Gwyther L, et al. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001;56:1154-66.
- Liperoti R, Mor V, Lapane KL, Pedone C, Gambassi G, Bernabei R. The use of atypical antipsychotics in nursing homes. *J Clin Psychiatry* 2003;64:1106-12.
- Health Canada, important drug safety information: RISPERDAL* (risperidone) and cerebrovascular adverse events in placebo-controlled dementia trials—Janssen-Ortho. www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/risperdal1_e.html (accessed 15 Nov 2004).
- Brodsky H, Ames D, Snowden J, Woodward M, Kirwan J, Clarnette R, et al. A randomized placebo controlled trial of risperidone for the treatment of aggression, agitation, and psychosis in dementia. *J Clin Psychiatry* 2003;64:134-43.
- Wooltorton E. Risperidone (Risperdal): increased rate of cerebrovascular events in dementia trials. *CMAJ* 2002;167:1269-70.
- 2003 Safety alert: RISPERDAL (risperidone). Washington, DC: US Food and Drug Administration; 1 Mar 2004. www.fda.gov/medwatch/SAFETY/2003/risperdal.htm (accessed 15 Nov 2004).
- Wooltorton E. Olanzapine (Zyprexa): increased incidence of cerebrovascular events in dementia trials. *CMAJ* 2004;170:1395.
- Atypical antipsychotic drugs and stroke: message from Professor Gordon Duff, Chairman, Committee on Safety of Medicines (CEM/CMO/2004/1). www.mca.gov.uk/ourwork/monitorsafequalmed/safetymessages/antipsychoke_9304.htm (accessed 15 Nov 2004).
- Gladstone DJ, Kapral MK, Fang J, Laupacis A, Tu JV. Management and outcomes of transient ischemic attacks in Ontario. *CMAJ* 2004;170:1099-104.
- Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA* 2000;284:2901-6.
- Coull AJ, Lovett JK, Rothwell PM. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. *BMJ* 2004;328:326-8.
- Hill MD, Yiannakoulis N, Jeerakathil T, Tu JV, Svenson LW, Schopflocher DP. The high risk of stroke immediately after transient ischemic attack: a population-based study. *Neurology* 2004;62:2015-20.
- Straus SE, Majumdar SR, McAlister FA. New evidence for stroke prevention: scientific review. *JAMA* 2002;288:1388-95.
- Schneeweiss S, Seeger JD, Maclure M, Wang PS, Avorn J, Glynn RJ. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. *Am J Epidemiol* 2001;154:854-64.
- Lee PE, Gill SS, Freedman M, Bronskill SE, Hillmer MP, Rochon PA. Atypical antipsychotic therapy in the treatment of behavioural and psychological symptoms of dementia: systematic review. *BMJ* 2004;329:75-8.
- Hollander M, Koudstaal PJ, Bots ML, Grobbee DE, Hofman A, Breteler MM. Incidence, risk, and case fatality of first ever stroke in the elderly population: the Rotterdam study. *J Neurol Neurosurg Psychiatry* 2003;74:317-21.
- Herrmann N, Mamdani M, Lanctôt KL. Atypical antipsychotics and risk of cerebrovascular accidents. *Am J Psychiatry* 2004;161:1113-5.
- Liperoti R. Cerebrovascular events among elderly patients treated with conventional or atypical antipsychotics. 2004 Annual meeting of the American Geriatrics Society. www.americangeriatrics.org/news/meeting/schedule_events.pdf (accessed 15 Nov 2004).
- Kozma CM, Engelhart LM, Long S, Greenspan A, Mahmoud R, Baser O. Absence of increased relative stroke risk in elderly dementia patients treated with risperidone versus other antipsychotics. 2003 meeting of the International College of Geriatric Psychoneuropharmacology. www.icgp.org/ICGP_2003_program_Book.pdf (accessed 15 Nov 2004).
- Smith DA, Beier MT. Association between risperidone treatment and cerebrovascular adverse events: examining the evidence and postulating hypotheses for an underlying mechanism. *J Am Med Dir Assoc* 2004;5:129-32.
- Wallaschofski H, Donne M, Eigenthaler M, Hentschel B, Faber R, Stepan H, et al. PRL as a novel potent cofactor for platelet aggregation. *J Clin Endocrinol Metab* 2001;86:5912-9.
- Harrison-Woolrych M, Clark DWJ. Nose bleeds associated with use of risperidone. *BMJ* 2004;328:1416.
- Zornberg GL, Jick H. Antipsychotic drug use and risk of first-time idiopathic venous thromboembolism: a case-control study. *Lancet* 2000;356:1219-23.
- Brown TM, Boyle MF. Delirium. *BMJ* 2002;325:644-7.
- Teri L, Logsdon RG, McCurry SM. Nonpharmacologic treatment of behavioral disturbance in dementia. *Med Clin North Am* 2002;86:641-56.
- Guidance for the management of behavioural and psychiatric symptoms in dementia and the treatment of psychosis in people with history of stroke/TIA. Working group for the Faculty of Old Age Psychiatry RCPsych, RCGP, BGS, and Alzheimer's Society, following CSM restriction on risperidone and olanzapine. www.bgs.org.uk/publications/CSM%20announcement%2009%2003%202004.pdf (accessed 15 Nov 2004).
- Schneider LS, Tariot PN, Lyketsos CG, Dagerman KS, Davis KL, Davis S. National Institute of Mental Health clinical antipsychotic trials of intervention effectiveness (CATIE): Alzheimer's disease trial methodology. *Am J Geriatr Psychiatry* 2001;9:346-60.

(Accepted 1 December 2004)

doi 10.1136/bmj.38330.470486.8F