

The metabolic side-effects of antipsychotics in elderly patients

Concerns have arisen that antipsychotic medication is associated with adverse metabolic effects, such as diabetes, weight gain, and dyslipidaemia. These drugs are used frequently in older people and as many as half of all prescriptions for antipsychotics are estimated to be for people older than 65 years. Furthermore, the incidence of diabetes and other metabolic disorders increases with age. Data from randomised controlled trials and observational studies suggest that the rate of adverse events is lower in older people on antipsychotics compared with younger individuals with schizophrenia. Nevertheless, taking precautions is important when using these drugs in elderly patients. Blood-glucose and lipid profiles should be checked before starting treatment, 3–4 months later, and then yearly.

Dr Richard Holt Reader of Endocrinology & Metabolism, Endocrinology & Metabolism Sub-division, Developmental Origins of Health and Disease, School of Medicine, University of Southampton, Southampton, UK.

email righ@soton.ac.uk

The introduction of antipsychotic drugs in the 1950s transformed the lives of many mentally ill people. Although conventional antipsychotics are highly effective, their use is marred by disabling and stigmatising movement disorders. Atypical antipsychotics were developed in an attempt to reduce these side-effects. Concerns arose, however, that atypical antipsychotics were associated with clinically significant weight gain and other related metabolic side-effects, including diabetes and dyslipidaemia. Additionally, some thought that the switch from conventional to atypical antipsychotics had merely led to the substitution of one set of side-effects for another.¹

Metabolic side-effects in elderly patients are an important consideration because the use of antipsychotic medication in this age group is remarkably common—despite warnings that these agents are associated with increased mortality rates in patients with dementia.² The use of antipsychotics in patients with dementia goes beyond the licence of these drugs, but has been recommended by groups such as a US Expert Consensus Panel.³ As many as half of all repeat prescriptions for antipsychotics are estimated to occur in people older than 65 years.⁴ Between 38–43% and 60–80% of all elderly patients living in nursing homes or old-age psychiatry units, respectively, receive antipsychotics. Around 20% of people aged older than 80 years are affected by dementia, and 25–50% of these patients develop psychotic symptoms requiring treatment.⁴

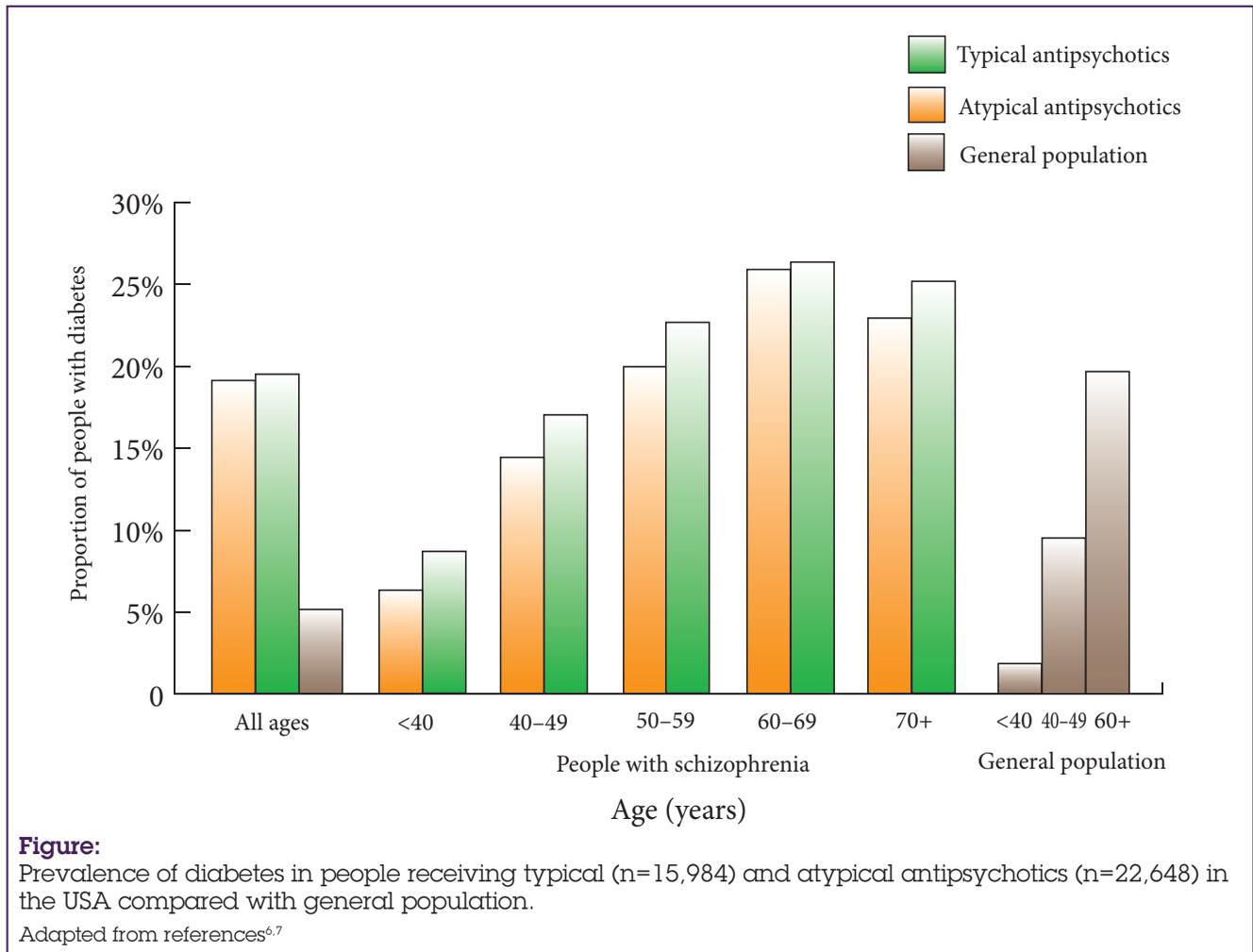
The prevalence of diabetes and dyslipidaemia increases with age, which is another reason that the metabolic side-effects of antipsychotics should be considered when treating elderly patients. Thus, even a small increase in the relative risk of metabolic problems may present a major clinical problem.

Investigating antipsychotic drugs and their metabolic side-effects

The debate about the role of antipsychotics in the aetiology of metabolic problems in schizophrenia has been considerable. Data from randomised controlled trials show no differences between various atypical antipsychotics, between atypical and conventional antipsychotics, or between antipsychotics and placebo. But in general, the quality of reporting of metabolic side-effects is poor and studies are underpowered and of insufficient duration to examine rare side-effects. The most powerful observational data come from large pharmacoepidemiological studies.

By including many thousands of patients, these studies have the power to detect small risks. They show that antipsychotics are associated with increases in metabolic side-effects, but the studies also have problems, and the conclusions drawn from them should be regarded with caution. Their lack of randomisation may mean that observed differences occur from bias in treatment assignment, screening rates, or baseline characteristics.¹

Most data come from studies of younger people with schizophrenia or bipolar illness, and how far these findings can be extrapolated to the treatment of older people, in whom the indications for antipsychotics and patient characteristics may differ, is unclear. However, a number of studies in elderly patients suggest that older people are less likely to be affected by metabolic side-effects than are younger people with schizophrenia.



Diabetes

The rates of diabetes in people with schizophrenia are increased 2–3 fold compared with the general population.⁵ The reasons for this increase include a combination of both genetic and environmental factors as well as the neuroendocrine changes of acute psychosis and the effects of drugs. Although diabetes occurs rapidly after the initiation of antipsychotic treatment in a few cases, the risk of developing diabetes as a result of antipsychotic treatment is low for most patients. Many of those who do develop the condition do so because of other reasons.¹

The greatest increase in risk of diabetes occurs in younger people and effects of the drugs seem lower in elderly people. In one US study, the rate of diabetes in those younger than 40 years on antipsychotics was similar to the US general population aged 40–60 years, and the rate of diabetes for antipsychotic users aged 40–50 was similar to the US general population aged older than 60 years

(figure).^{6,7} The same study showed that prevalence among people on antipsychotics reached a plateau around the 7th decade and began to drop after 70 years.⁶

A large longitudinal retrospective study examined the incidence of new diabetes medication in more than 30,000 people older than 60 years receiving antipsychotic drugs.⁴ New prescriptions were around 3-fold higher in those taking antipsychotics compared with healthy elderly people, but no differences were seen between conventional and atypical antipsychotics. When the study was further stratified by age, the risk seemed higher in patients aged 60–74 years than in those older than 75 years. This finding is important because a higher proportion of patients in the older group had prescriptions for antipsychotics.

Drawing firm conclusions about effects of antipsychotics from these studies is difficult because of the differences in baseline characteristics between those receiving antipsychotics and the general population. Perhaps, a fairer comparison would be to examine the diabetes rates in those receiving different classes of drugs for similar

indications. Making an accurate assessment from large databases for such a comparison is complicated, but a Canadian retrospective cohort study of more than 11,000 patients older than 65 years compared incidence of diabetes in those prescribed atypical or typical antipsychotics with those on benzodiazepines or corticosteroids.⁸ The figures were 47, 31, and 40 per 1,000 patient years for patients treated with typical antipsychotics, atypical antipsychotics, and benzodiazepines, respectively, which was significantly lower than for those treated with corticosteroids (190 per 1,000 patient years). No differences in incident diabetes were found between those receiving antipsychotics and those on benzodiazepines, and subanalysis showed no differences between atypical antipsychotics.

In a smaller cross-sectional study of 99 elderly patients with Alzheimer's disease, blood-glucose concentrations were similar between those receiving antipsychotic medication and those who did not.⁹ Another small study, of patients with Parkinson's disease treated with clozapine, discovered that the prevalence of diabetes was 18.1%, which was similar to that of the age-matched general population.¹⁰

Randomised controlled trials are also reassuring about the risk of diabetes. A study examining the efficacy of different atypical antipsychotics for Alzheimer's disease in 421 elderly patients found no change in blood glucose over 36 weeks in any of the treatment or placebo groups.¹¹ The power of this study, however, was substantially limited by the high discontinuation rate; after 36 weeks, only about 20% were still taking their assigned medication.

A pooled analysis of the incident diabetes rates in seven olanzapine clinical trials, each lasting 2–6 months, in 1,678 patients older than 65 years of age with Alzheimer's disease, vascular dementia, or mixed dementia noted that, overall, 2.1% developed diabetes with no difference between the antipsychotic and placebo groups.¹² The only predictor of treatment-emergent diabetes was baseline blood glucose and, interestingly, baseline body-mass index and clinically significant weight gain did not predict diabetes. Overall, the studies suggest that the risk of diabetes with use of antipsychotics is low in elderly patients.

Weight gain

Weight gain is a common side-effect of atypical antipsychotics, but the underlying reason is unclear and probably involves several mechanisms. A meta-analysis of randomised controlled trials in younger patients showed that the mean weight gain was greatest for clozapine and olanzapine (>4 kg) but other drugs, such as risperidone and quetiapine, caused less weight gain.¹³ Observational studies have confirmed this pattern of weight gain but

overall have shown less weight gain over longer periods of time¹⁴—probably because in clinical practice, psychiatrists and patients frequently choose to switch drugs when weight gain becomes a problem.

In elderly patients with dementia, weight loss is a more common clinical problem than is weight gain.¹⁵ Food intake declines with ageing and unintentional weight loss may occur. About 5–12% of community-dwelling elderly people are underweight and this figure rises to 20–54% of those in residential care.¹⁶

The risk of weight gain with antipsychotics seems to be smaller in elderly patients than in younger people. Over a 6-week study of patients with Alzheimer's disease, the average weight gain for people treated with olanzapine was 0.8 kg compared with a small weight loss for placebo-treated patients.¹⁷ A 10-week placebo-controlled study of aripiprazole in psychosis in Alzheimer's disease found that mean weight changes were comparable between aripiprazole and placebo-treated patients, with less than 5% reporting more than 7% weight gain in either group.¹⁸ Neither quetiapine nor risperidone were associated with weight change in a further 8-week study,¹⁹ and a meta-analysis of five studies comparing olanzapine with placebo in elderly patients noted a mean weight gain of only 0.9 kg over a 2–3 month period.²⁰

Observational studies have similar findings: a naturalistic follow-up study showed a 2% weight gain in patients treated with quetiapine over 4 weeks.²¹ Another retrospective study of 99 patients with Alzheimer's disease in long-term residential care⁹ showed no difference in body-mass index between those receiving atypical antipsychotics and those who were not. Therefore, weight gain seems much less marked in older people on atypical antipsychotics compared with younger people.

Dyslipidaemia

Clinical studies of lipid effects of antipsychotics suggest a moderate adverse effect on low-density-lipoprotein cholesterol and high-density-lipoprotein cholesterol, with little difference between drugs.²² By contrast, the effect on triglyceride concentrations is more marked, and appears to mirror changes in body weight. In the aforementioned small study of 99 patients with Alzheimer's disease, lipid profile was the same for those receiving atypical antipsychotics and those who were not.⁹ But, a 4-week observational study of people treated with quetiapine did show a modest 8.9% increase in triglycerides.²¹

No major concerns have been raised in prospective studies. The study of different atypical antipsychotics in Alzheimer's disease did not find a significant change in

serum cholesterol or triglycerides between treatments.¹¹ Furthermore, in a meta-analysis of the adverse events in six trials of olanzapine in Alzheimer's disease, no significant change in triglycerides were seen with the drug, and total cholesterol actually fell slightly in patients on olanzapine.¹² A 6-month study²³ of olanzapine in elderly patients with schizophrenia also did not find a change in cholesterol or triglyceride concentration compared with those not on the drug.

Clinical implications

The current population based evidence about the metabolic safety of these medications in elderly people is reassuring. Nevertheless, recognising that adverse events may occur in individual cases is important. Therefore, taking the same precautions for elderly patients as you would do for younger patients when using antipsychotics seems sensible. Blood-glucose and lipid profiles should be checked before starting treatment, 3–4 months later, and then annually.²⁴

Conclusions

There are concerns that atypical antipsychotics are associated with adverse metabolic effects. These drugs are widely used in elderly patients in several clinical settings and therefore, an appreciation of these risks is important. Evidence suggests that the risk in older people is less than for younger people with schizophrenia. Nevertheless, undertaking regular monitoring of weight and, glucose and lipid profiles in older people on antipsychotics would be prudent.

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References

- Holt RI, Peveler RC. Antipsychotic drugs and diabetes—an application of the Austin Bradford Hill criteria. *Diabetologia* 2006; **49**: 1467–76
- 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**: 1934–43
- Alexopoulos GS, Streim J, Carpenter D, Docherty JP. Using antipsychotic agents in older patients. *J Clin Psychiatry* 2004; **65** (Suppl 2): 5–99
- Feldman PD, Hay LK, Deberdt W, Kennedy JS, et al. Retrospective cohort study of diabetes mellitus and antipsychotic treatment in a geriatric population in the United States. *J Am Med Dir Assoc* 2004; **5**: 38–46
- Holt RI, Bushe C, Citrome L. Diabetes and schizophrenia 2005: are we any closer to understanding the link? *J Psychopharmacol* 2005; **19** (6 Suppl): 56–65
- Sernyak MJ, Leslie DL, Alarcon RD, et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry* 2002; **159**: 561–66
- Diabetes Public Health Resource, Division of Diabetes Translation. Centers for Disease Control and Prevention. Data and trends. National Diabetes Surveillance System. Total prevalence of diabetes among people aged 20 years or older, United States, 2002. <http://www.cdc.gov/diabetes/pubs/estimates.htm#fig2> (date accessed 9 June 2008)
- Etminan M, Streiner DL, Rochon PA. Exploring the association between atypical neuroleptic agents and diabetes mellitus in older adults. *Pharmacotherapy* 2003; **23**: 1411–15
- Rondanelli M, Sarra S, Antonello N, Mansi V, Govoni S, Falvo F et al. No effect of atypical antipsychotic drugs on weight gain and risk of developing type II diabetes or lipid abnormalities among nursing home elderly patients with Alzheimer's disease. *Minerva Med* 2006; **97**: 147–51
- Fernandez HH, Friedman JH, Lansang MC, Factor SA, Molho ES, Coskun DJ. Diabetes mellitus among parkinsonian patients treated chronically with clozapine. *Parkinsonism Relat Disord* 2004; **10**: 439–41
- 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**: 1525–38
- Micca JL, Hoffmann VP, Lipkovich I, Ahl J, Baker RW, Hardy TA. Retrospective analysis of diabetes risk in elderly patients with dementia in olanzapine clinical trials. *Am J Geriatr Psychiatry* 2006; **14**: 62–70
- Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, et al. Antipsychotic-induced weight gain: a comprehensive synthesis. *Am J Psychiatry* 1999; **156**: 1686–96
- Haro JM, Salvador-Carulla L. The SOHO (Schizophrenia Outpatient Health Outcome) study: implications for the treatment of schizophrenia. *CNS Drugs* 2006; **20**: 293–301
- Henderson AS. The social psychiatry of later life. *Br J Psychiatry* 1990; **156**: 645–53
- Kennedy JS, Bymaster FP, Schuh L, Culligaro DO, Nomikos G, Felder CC et al. A current review of olanzapine's safety in the geriatric patient: from pre-clinical pharmacology to clinical data. *Int J Geriatr Psychiatry* 2001; **16** Suppl 1: S33–61
- Street JS, Clark WS, Gannon KS, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group. *Arch Gen Psychiatry* 2000; **57**: 968–76
- De Deyn PP, Jeste DV, Swaminik R, et al. Aripiprazole for the treatment of psychosis in patients with Alzheimer's disease: a randomized, placebo-controlled study. *J Clin Psychopharmacol* 2005; **25**: 463–67
- Rainer M, Haushofer M, Pfohl H. Quetiapine versus risperidone in elderly patients with behavioural and psychological symptoms of dementia: Efficacy, safety and cognitive function. *Eur Psychiatry* 2007; **22**: 395–403
- Kryzhanovskaya LA, Jeste DV, Young CA, et al. A Review of Treatment-Emergent Adverse Events During Olanzapine Clinical Trials in Elderly Patients With Dementia. *J Clin Psychiatry* 2006; **67**: 933–45
- Yang CH, Tsai SJ, Hwang JP. The efficacy and safety of quetiapine for treatment of geriatric psychosis. *J Psychopharmacol* 2005; **19**: 661–66
- Bushe C, Paton C. The potential impact of antipsychotics on lipids in schizophrenia: is there enough evidence to confirm a link? *J Psychopharmacol* 2005; **19**(6 Suppl): 76–83
- Barak Y, Shamir E, Zemishlani H, et al. Olanzapine vs. haloperidol in the treatment of elderly chronic schizophrenia patients. *Prog Neuropsychopharmacol Biol Psychiatry* 2002; **26**: 1199–202
- Metabolic and lifestyle issues and severe mental illness—new connections to well-being. *J Psychopharmacol* 2005; **19** (6 Suppl): 118–22