

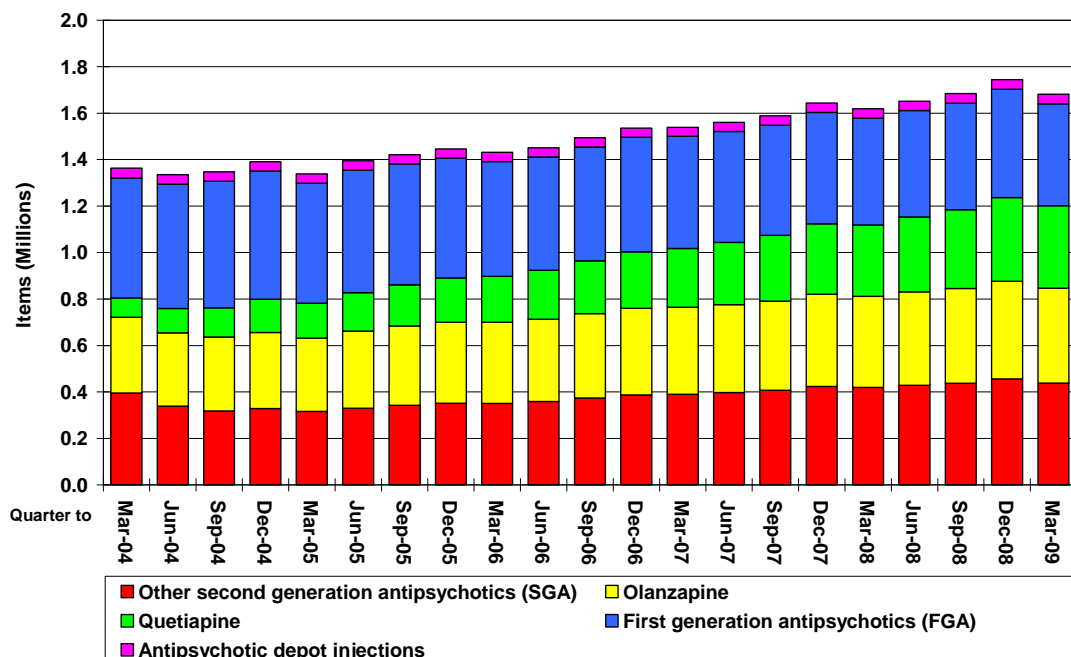
Antipsychotic drugs

Antipsychotics can be broadly classified into first generation antipsychotics (FGAs, formerly known as ‘typical’ antipsychotics) and second generation antipsychotics (SGAs, formerly known as ‘atypical’ antipsychotics). They are used for managing disturbed patients whether the underlying psychopathology is schizophrenia, agitated depression, mania or brain damage. The potency of most antipsychotics is directly proportional to their ability to block dopamine receptors in the brain. However, many also have significant effects on acetylcholine, norepinephrine, histamine and serotonin receptors.^{1,2}

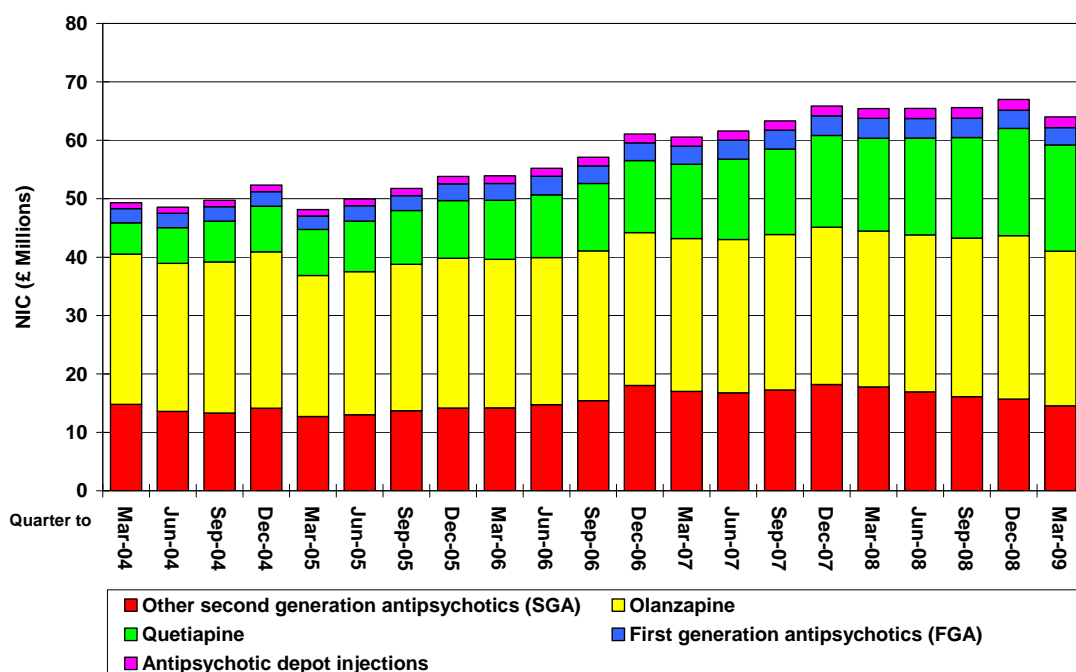
Selection of FGAs (e.g. chlorpromazine, haloperidol, fluphenazine and flupentixol) is influenced by the degree of sedation required and the variability in patient susceptibility to the main adverse events: extrapyramidal side effects (EPSEs), hyperprolactinaemia, and metabolic side effects. SGAs (e.g. quetiapine, olanzapine, risperidone) have a different propensity to cause the same range of side effects to FGAs; the main difference between the two is the therapeutic index in relation to EPSEs.¹

Clozapine is reserved for people with schizophrenia which has not responded well to the sequential use of two or more antipsychotics (one of which should be an SGA) each for at least 6–8 weeks.² Depot antipsychotics are used for maintenance therapy, especially when patients have difficulty complying with oral medication. They are usually initiated in hospital but use is continued by the community mental health team. There are five FGA depot injections available but risperidone is the only SGA available as a long-acting injection.

Trends in Prescribing of Antipsychotic Drugs in General Practice in England (Chart 1)



Trends in Spending on Antipsychotic Drugs in General Practice in England (Chart 2)



Charts 1 and 2 show that prescribing of SGAs exceeds that of FGAs thus reflecting recommendations made in the first NICE Schizophrenia Guideline (2002) to prescribe SGAs in preference to FGAs. In addition, licence extensions in the treatment of bipolar disorder for some of the SGAs such as risperidone, olanzapine and quetiapine could have led to an increase in their prescribing. Currently, oral SGAs account for 73% of antipsychotic items prescribed and 95% of the total cost. It is also worth noting that there may be significant prescribing via the hospital prescription route for oral and depot antipsychotics depending on local patterns of service delivery, which is not captured in this data.

Schizophrenia

Premature mortality in people with schizophrenia exceeds that of the general population by approximately 50%. This is due partly to a wide range of physical health problems; these include those induced by cigarette smoking (which is more prevalent in this population), obesity and diabetes.³ This tendency towards increased cardiovascular risk may be compounded by metabolic adverse effects such as weight gain, hyperglycaemia and diabetes which are associated with both FGAs and SGAs. Two seminal randomized controlled trials, CATIE and CUtLASS were published after the first NICE Schizophrenia guideline.^{4,5} CUtLASS showed there was no evidence that people receiving FGAs vs SGAs would experience any disadvantage in terms of quality of life, symptoms or associated costs of care, and CATIE also suggested that there is little to choose in terms of overall tolerability and effectiveness between the FGAs and SGAs studied. The new NICE Schizophrenia guideline 82 now recommends that all people with newly diagnosed schizophrenia should be offered antipsychotic medication but, unlike the previous guideline, makes no recommendation with regard to the preferred use of SGAs over FGAs. It recommends that the choice of drug

should be made jointly between the patient and the health professional taking into account the views of the carer. The relative likelihood for individual antipsychotic drugs to cause EPSEs, metabolic side effects and other side effects should also be considered. NICE recommends treatment with an antipsychotic should be considered equivalent to an individual therapeutic trial; thus the following should also be recorded: the indications; expected benefits and risks; expected time for a change in symptoms and for side-effects to occur. Also any dosages outside the licensed range need to be justified and recorded, and notes made of efficacy, side effects, adherence and physical health.³

NICE recommends health professionals should monitor physical health at least once a year and copy the results to the secondary care coordinator. This process should be proactively managed. Recently a cohort analysis carried out in the US compared clinician monitoring rates of plasma lipid and glucose in people taking antipsychotics before and after guidelines were issued by the American Diabetes Association, and found that these remained alarmingly low despite US government endorsement.⁶

Agitated behaviour in the elderly

In 2004 the Committee on Safety of Medicines (now the Commission on Human Medicines) first reported a clear increase in the risk of stroke with the use of risperidone and olanzapine in elderly people with dementia. A year later a Europe-wide review concluded that the risk could not be excluded for other SGAs or FGAs.⁷ An extended follow-up (up to 54 months) of the dementia antipsychotic withdrawal trial (DART-AD) found that patients with Alzheimer's dementia who continued to use antipsychotics were more likely to die than those taking placebo (at 24 months' survival: 46% vs 71%, respectively; 36 months' survival 30% vs 59%, respectively).⁸ Recent warnings issued by the European Medicines Agency and the Medicines and Healthcare products Regulatory Authority both reiterated the 'increased risk of stroke and a small increased risk of death when any antipsychotics are used in elderly people with dementia'.^{7,9} The NICE-SCIE guidance on dementia advises that antipsychotics are only to be used in exceptional circumstances in such patients and, in its recent National Dementia Strategy, the Department of Health has included an audit tool to help organizations monitor practice.^{10,11}

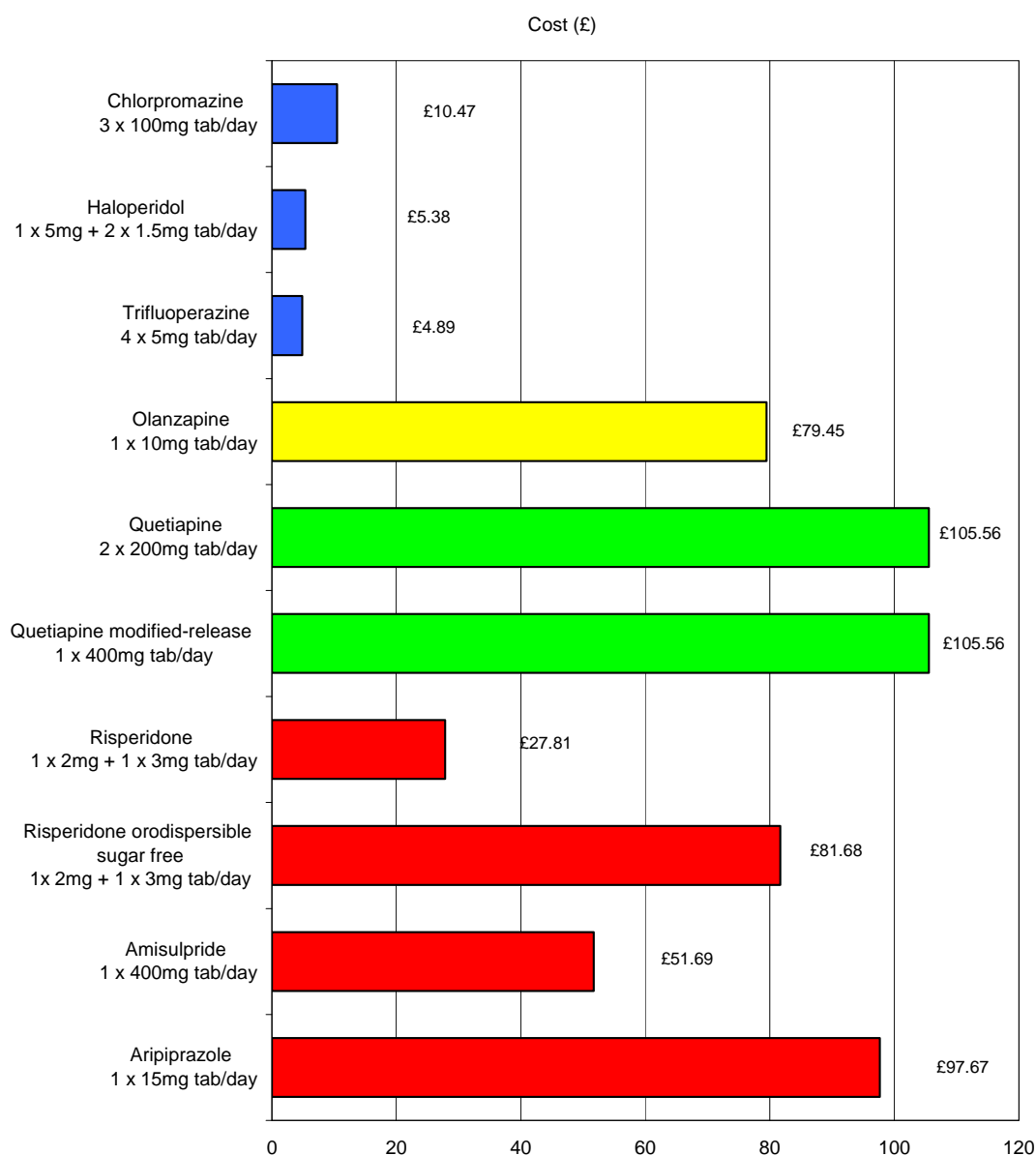
Prescribing Data

(Reporting quarter = Jan–Mar 2009, Index quarter = Jan-Mar 2004)

Prescribing of antipsychotic drugs (excluding depot injections) has increased by 24% in the last five years to 1.6 million items per quarter, and costs have increased by 29% to £62.2 million. Prescribing of SGAs (excluding depot injections) has risen by 49% to 1.2 million items and costs by 29% to £59.2 million. Prescribing of FGAs (excluding depot injections) has decreased 15% to 439,000 items, whereas the cost has risen by 21% to £2.9 million. Chlorpromazine is the most commonly prescribed FGA (117,000 items, £694,000). However, its prescribing has fallen by 28% and its cost has more than doubled. Prescribing of haloperidol (excluding depot injections) has increased 16% to 107,000 items with the cost decreasing by 7% to £437,000.

Prescribing of antipsychotic depot injections remains constant at 41,000 items (a 2% decrease), but in the last five years their cost has risen to £1.8 million (a 79% increase). The most commonly prescribed depot injection is flupentixol decanoate (15,000 items, £210,000) but items and spend have decreased by 17% and 33% respectively. However, prescribing of risperidone depot injections has quadrupled to 7,000 items (£1.3 million).

Cost for 28 Days Treatment



Prices based on Drug Tariff August 2009 or Chemist and Druggist August 2009. Dose based on WHO DDDs where possible, otherwise BNF stated dose. The WHO DDD is a unit of measurement based on the assumed average maintenance dose in adults. It may not necessarily reflect the actual dose used.

Table 1 shows the percentage of items prescribed, by strength, for the top three most prescribed SGAs in primary care in the quarter to March 2004 compared with quarter to March 2009. Oral risperidone is the only antipsychotic licensed for the short-term treatment (up to 6 weeks) of

dementia-related behavioural disturbances in people with Alzheimer's dementia who are unresponsive to non-pharmacological measures. Over the last five years there has been a drop in the total prescribing of risperidone by 20% (to 280,000 items per quarter), and a 52% decrease in risperidone 500microgram tablets/orodispersible tablets. Olanzapine is the most commonly prescribed SGA (408,000 items). Prescribing of olanzapine has increased by 25% while cost has risen by 3% (to £26.5 million). The most commonly prescribed strength of oral olanzapine is 10mg tablets (155,000 items costing £12.7million), followed by 5mg tablets (123,000 items costing £5.9million). The lowest oral strength (2.5mg) has increased by 8% to 69,000 items; costs fell by 7% to £2.2million. The prescribing of quetiapine has quadrupled and now stands at 355,000 items, with cost more than trebling to £18.2 million per quarter. The most commonly prescribed presentation of quetiapine is the low strength 25mg tablet (188,000 items, £5.4 million), followed by 100mg tablets (55,000 items, £3.9 million). The impact of the new NICE Schizophrenia Guideline, the National Dementia Strategy and the recent reports in the medical press should be noticeable in future prescribing patterns.

Breakdown of prescribing by strength for the top three SGAs (Table 1)

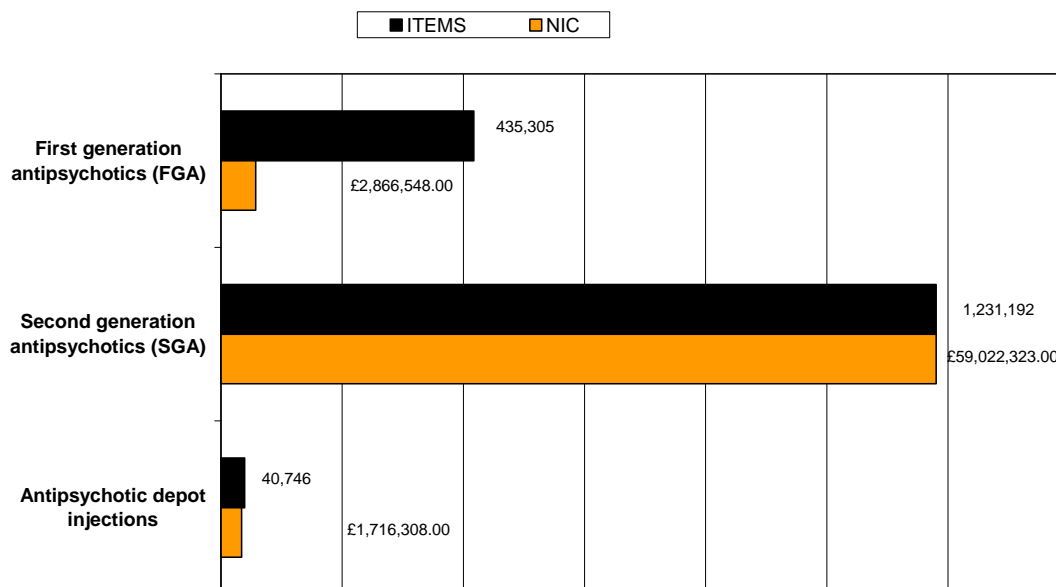
	% of total items Qtr to Mar 04	% of total items Qtr to Mar 09
Risperidone 500mcg tab / Orodispersible tab	40	24
Risperidone 1mg tab / Orodispersible tab	29	30
Risperidone 2mg tab / Orodispersible tab	14	22
Risperidone 3mg tab / Orodispersible tab	6	9
Risperidone 4mg tab / Orodispersible tab	6	9
Risperidone 6mg tab	1	2
Total Oral Risperidone Items	351,305	280,162
Olanzapine 2.5mg tab	20	17
Olanzapine 5mg tab / oral lyophilisate tab	32	30
Olanzapine 7.5mg tab	5	5
Olanzapine 10mg tab / oral lyophilisate tab	39	38
Olanzapine 15mg tab / oral lyophilisate tab	4	5
Olanzapine 20mg tab / oral lyophilisate tab	0	5
Total Oral Olanzapine Items	325,864	408,169
Quetiapine 25mg tab	45	53
Quetiapine 100mg tab	18	16
Quetiapine 150mg tab	16	7
Quetiapine 200mg tab	18	12
Quetiapine 300mg tab	2	8
Total Oral Quetiapine Items	84,143	354,826

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10. NICE Dementia. Clinical Guideline 42. November 2006. www.nice.org.uk/nicemedia/pdf/CG42Dementiafinal.pdf
11. National Dementia Strategy www.dh.gov.uk/en/SocialCare/Deliveringadultsocialcare/Olderpeople/NationalDementiaStrategy/index.htm

Summary

- Antipsychotics have diverse pharmacological actions and side effect profiles.
- NICE recommends that treatment with antipsychotics should be individualized and take account of the patient's and carer's views.
- All people with schizophrenia should have their physical health monitored once a year.
- Inappropriate use of antipsychotics in elderly people with dementia has been clearly shown to increase the risk of stroke.
- Risperidone is the only antipsychotic licensed for short-term (maximum 6 weeks) management of persistent aggression in elderly people with Alzheimer's dementia.

**Prescribing and Spending on Antipsychotic Drugs in England
for Quarter to June 2009**



Quarter to June 09

National

	ITEMS/1000 PUs	NIC/1000 PUs
Chlorpromazine	1.59	£8.96
Haloperidol	1.46	£5.99
Other first generation antipsychotics (FGA)	2.98	£24.88
Olanzapine	5.73	£356.27
Quetiapine	5.11	£265.05
Other second generation antipsychotics (SGA)	6.26	£199.21