

Cost-effectiveness of an **atypical conventional antipsychotic** in South Africa

An economic evaluation of quetiapine versus haloperidol in the treatment of patients partially responsive to previous antipsychotics

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Background. The introduction of a new generation of atypical antipsychotic agents has raised difficult economic and ethical questions, particularly in lower-income countries. The reported tolerability and efficacy advantages of the atypical antipsychotics over their conventional predecessors have to be weighed against their higher acquisition costs. Pharmacoeconomic studies conducted in Western countries consistently report cost advantages or cost neutrality for these new agents. However, considerable differences in health care service provision make it difficult to generalise these findings to South Africa.

Method. We compared the direct costs (private and public sector) of treating schizophrenia with an atypical antipsychotic quetiapine, and with a conventional antipsychotic haloperidol, by adapting a decision-analytic pharmacoeconomic model for South African circumstances. The sample comprised patients partially responsive to antipsychotics, who had participated in a multinational randomised controlled trial comparing the efficacy and safety of quetiapine versus haloperidol.

Results. The estimated total direct cost for the treatment with quetiapine in South Africa was slightly less than for haloperidol for various models in both the private and the public sectors.

Conclusions. Significant differences in health care provision make pharmacoeconomic studies conducted in other coun-

tries invalid for South African circumstances. Previously quetiapine treatment did not result in direct cost savings in South Africa. However, the recently introduced legislation to establish single exit prices for medications has resulted in the cost of quetiapine treatment declining by 36.7% and that of haloperidol by 13%. This has translated into an overall direct cost saving for quetiapine in both the private and public sector models. This, together with additional indirect advantages of the atypical antipsychotics such as improved quality of life and better social and vocational functioning, argues strongly from both an economic and ethical perspective for the use of atypical antipsychotics in treating schizophrenia in South Africa.

Schizophrenia is one of the most important diseases affecting humankind, costly in both social and financial terms.¹ It imposes a disproportionately large economic burden on patients, their families, health care systems and society because of its early onset, devastating effects, and usually lifelong course,² and it is the most costly illness that psychiatrists treat.³ In 1993 the disease consumed an estimated \$33 billion in the USA (\$18 billion in direct costs and \$15 billion in indirect costs). This constituted 2.5% of the annual total health care allocations.⁴ In England, the identifiable direct and indirect costs suggest an annual total cost of £2.6 billion (this figure omitted some indirect costs).⁵ In South Africa the costs are not known. The direct costs of schizophrenia include aspects such as hospitalisation, day care, residential accommodation, medication, special investigations and disability grant payments. Examples of indirect costs are lost employment, reduced productivity and family costs (e.g. household expenditure, travel costs and lost earnings).⁶

In the current worldwide cost-cutting climate in health services, the focus has fallen on economising the delivery of health care. Yet decreasing expenditures on drugs for severe illnesses such as schizophrenia may be a false economy, as drugs account for only

a small proportion of the total costs.¹ In the case of schizophrenia the acquisition costs of medication comprise a very small portion of the total costs of the illness — at least in the developed world. For example, the costs of antipsychotic medication have been estimated at 4% of the direct costs in the UK,⁷ 5.6% in France,⁸ and 1.1% in the Netherlands.⁹

The introduction of the atypical antipsychotics has had a major impact on the way we treat patients with schizophrenia. Evidence is accumulating to show that these drugs hold significant advantages over their predecessors in terms of both tolerability (although other side-effect concerns have emerged) and efficacy. In particular, it has been shown that these agents have a reduced propensity to induce acute extrapyramidal symptoms (EPSs),¹⁰ previously a major obstacle to the effective treatment of schizophrenia. There is now a considerable literature indicating other advantages of these drugs. These advantages include improved efficacy in treatment-refractory patients,¹¹ in patients with negative symptoms¹² and depressive symptoms,^{13,14} reduced levels of suicidality,¹⁵ less neurocognitive impairment,¹⁶ better subjective quality of life,¹⁷ reduced incidence of tardive dyskinesia,¹⁸ decreased likelihood of relapse¹⁹ and improved overall outcome.²⁰ Although often modest, these advantages often make a substantial difference to patients in terms of improved social and vocational functioning and a better quality of life. The clinical advantages of these drugs are greatest close to the onset of the illness, and they are increasingly regarded as first-choice agents.²¹ However, because of their much greater acquisition costs, their availability in lower-income countries in regions such as Africa, Latin America, Asia and the Pacific is extremely limited.

Pharmaco-economic studies generally show the atypical antipsychotics to be cost-effective or cost-neutral in treating schizophrenia. But it is not clear to what degree these findings (conducted in the Western world) can be generalised to other countries, where other factors need to be considered. For example, schizophrenia reportedly runs a different course in developing countries,²² and a cost-effectiveness study in Nigeria indicated that the antipsychotic drugs accounted for 52.8% of the cost of treating schizophrenia!²³ This was because most patients are cared for by their families at no direct cost to the state, and residential care, when available, had low staff and infrastructure expenditure.

The ideal pharmaco-economic study would be a prospectively designed trial in a large sample, and conducted over a long study period. Such a study would however be very difficult to conduct, and extremely expensive. A less dependable but more easily attainable alternative is to construct a pharmaco-economic model

specifically for South African conditions. This study attempts to quantify the direct costs involved in treating a large group of patients with schizophrenia in South Africa. It will hopefully provide guidance to clinicians and decision makers alike regarding both private and public health sector costing.

Method

This study incorporated the clinical findings of a randomised controlled trial in a pharmaco-economic model adapted for South African circumstances. The model estimated outcomes and direct costs over 5 years for quetiapine and haloperidol in treating partially responsive patients with schizophrenia. Persistent positive symptoms occur in many patients treated with conventional antipsychotics,^{24,25} and this population has been referred to as 'partial responders'.²⁶ They are an important patient group, as they represent the majority of patients with schizophrenia, and their treatment is problematic. Consequently, disproportionately more resources are likely to be allocated to these patients.

Patients and study design

The study that we utilised for the analysis was a multicentre, double-blind, randomised trial comparing quetiapine and haloperidol in patients with a partial response to conventional antipsychotic treatment. Although multinational, many of the participants were in South Africa. A detailed description of the study design, patient selection criteria, and efficacy and safety measures has been reported elsewhere,²⁷ and so will only be briefly described here. Patients meeting the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed) (*DSM-IV*) diagnostic criteria for schizophrenia and who had a history of only partial response to conventional antipsychotics were entered into a 4-week active run-in treatment phase with fluphenazine (20 mg/day). Those patients showing either no response, or only a partial response to the fluphenazine treatment (defined as < 30% reduction in the Positive and Negative Symptom Scale (PANSS) total score), were then randomised to receive either quetiapine (600 mg/day) or haloperidol (20 mg/day). As these patients were envisaged to be difficult to treat, the quetiapine and haloperidol dosages were towards the upper end of their recommended dosage ranges, namely 600 mg/day and 20 mg/day, respectively. Current clinical practice with quetiapine has moved towards the use of considerably higher doses. In fact, 600 mg/day is usually the target dose for most patients, not just those considered difficult to treat. Doses were titrated over a 7-day period, and then fixed for the next

7 weeks. Key exclusion criteria included severe resistance to conventional antipsychotics, known non-responders to clozapine and an acute psychotic exacerbation within the past 3 months.

The results of the analysis of the intent-to-treat (ITT) population indicated that both quetiapine and haloperidol were associated with significant mean reductions in PANSS total scores. The reduction was numerically greater with quetiapine than that observed with haloperidol, but the difference did not reach statistical significance. However, the treatment response rate was significantly greater for quetiapine (52% v. 38%, $p = 0.04$). (Treatment response was defined as a reduction in PANSS total score of $\geq 20\%$ from week 4 to week 12). Further analysis on the ITT population indicated that a decrease in PANSS total score of $\geq 30\%$ from week 4 to week 12 was also in favour of quetiapine (29% v. 16%, $p = 0.01$). This can be seen as a good level of clinical response.²⁸ The results of the safety analysis indicate that the proportion of patients who were using anticholinergic medication at the end of the trial (after 8 weeks on either quetiapine or haloperidol) was significantly lower in the quetiapine group than the haloperidol group (32% v. 53%, respectively, $p = 0.001$). Other measures of EPS occurrence consistently indicated a lower incidence of EPS in the quetiapine group compared with the haloperidol group.

The pharmaco-economic model

We adapted a study that was previously conducted on this sample for UK circumstances.²⁹ Medical resource utilisation and unit costs were obtained for the South African private and public sectors. For the model, a decision-analytic model with Markov processes was constructed, incorporating the consequences of treatment with regard to both the treatment response and the incidence of EPS. The Markov model has been extensively used in pharmaco-economic studies.³⁰ Costs are computed on the basis of assumptions about service utilisation derived from the results of a randomised, controlled trial, the pattern of resource use assumed in South Africa and from information provided by South African psychiatrists. Five groups of patients are advanced through a Markov process of 11 health states in cycles of 3 months over a period of 5 years, based on the likely sequelae of relapse and non-response. These groups have different responses to medication and/or incidence of EPS. The sequelae for these groups are driven mainly by the probabilities of compliance to medication and relapse (determined from a literature review and advice from a panel of South African psychiatrists). The health states in the Markov model are as follows: PANSS improvement $> 30\%$ (without EPS); PANSS improvement $> 30\%$ (with EPS);

PANSS improvement $> 20\%$ but $< 30\%$ (without EPS); PANSS improvement $> 20\%$ but $< 30\%$ (with EPS); no treatment response (PANSS improvement $< 20\%$); first relapse; post-relapse (quetiapine treatment): response (PANSS $> 30\%$); post relapse (haloperidol treatment): response (PANSS $> 30\%$); post-relapse: no response (PANSS $< 30\%$); subsequent relapse(s); suicide.

Results

The original model for the UK found the total treatment costs for quetiapine to be lower than those for haloperidol. While the cost of medication was higher for quetiapine-treated patients, substantial cost savings were achieved by a reduction in the use of health care services. It cost £244 less per patient over the 5-year period for the quetiapine-treated patients than for those treated with haloperidol (£38 106 v. £38 350).²⁹ However, these findings cannot be generalised to South Africa as substantial differences exist between psychiatric service delivery in the UK and both the private and public sectors in South Africa. Health care costs obtained in August 2004 for the private and public sectors in South Africa are provided in Tables I and II respectively. Medication costs in South Africa subsequent to August 2004 are provided in Table III. Costs between countries differ not only in terms of fee structures for specific items, but also regarding their nature. For example, general practitioners and community nurses are much less frequently involved in treating patients with schizophrenia in the private sector in South Africa than in the UK. Also, daycare and residential care facilities are less available in both the private and public sectors. Therefore, although these costs are saved in the South African system, the absence of these services increases the likelihood of relapse and lengthens the duration of hospitalisation. On the basis of information obtained from a panel of South African psychiatrists from both the private and public sector, we made certain assumptions regarding these differences, and calculated the following solutions: (i) 'baseline' situation — this was a direct transposition of South African private sector costs in the original model without making other assumptions about differences in health care provision between the UK and SA; (ii) 'private sector 1' situation — assumed a 5% increase in hospitalisation and risk of relapse for private health care services in South Africa; (iii) 'private sector 2' situation — assumed a 10% increase in hospitalisation and risk of relapse for private health care services in South Africa; (iv) 'public sector 1' situation — assumed a 5% increase in hospitalisation and risk of relapse for public health care services in South Africa; and (v) 'public sector 2' situation — assumed a 10% increase in hospitalisation and risk of relapse for public health care services in South Africa.

Table I. Private psychiatric care costs in South Africa*

Item	Cost per day (R)
Hospital admission bed day (acute stay)	725.60
Hospital admission bed day (long stay)	681.10
Residential care (1 day)	130.00
Psychiatrist consultation (25 minutes)	214.10
GP consultation	117.20
Psychiatric nurse visit (1 hour)	73.40
Day care	486.00
Outpatient visit	255.90

* Data provided by Old Mutual Health Group, and based on previous Board of Healthcare Funders tariffs, August 2004.

Table II. Public psychiatric care costs in South Africa*

Item	Cost per day (R)
Inpatient care (acute stay)	680.00
Inpatient care (long stay)	460.00
Psychiatrist visits (25 minutes)	180
Outpatient visits	180
Community psychiatry visits	125
GP (clinic) visits	125

* Source: Uniform Patient Fee Schedule for externally funded patients attending public hospitals of the Provincial Administration of the Western Cape, 1 January 2004.

Table III. Medication costs in South Africa*

Product	Trade price (R)	Pack size	Dosage/day	Cost/day (R)
Quetiapine 300 mg	1 017.54	60	600 mg	33.92
Haloperidol 5 mg	229.04	100	20 mg	9.16
Olanzapine 10 mg	965.78	28	20 mg	68.98
Risperidone 4 mg	928.12	30	8 mg	61.87
Clozapine 100 mg	682.56	100	600 mg	40.95
Artane 2 mg	62.28	100	2 mg	0.62
Akineton 2 mg	86.21	50	2 mg	1.72
Akineton 5 mg/ml	121.35	5	5 mg/ml	24.27
Fluoxetine 20 mg (Prozac)	193.85	30	20 mg	6.46
Lilly-Fluoxetine (generic)	72.10	28	20 mg	2.58

* Source: Pharmaceutical Computer Data, August 2004. Prices are trade prices excluding VAT and pharmacy costs.

The results of the cost-effectiveness analysis for each of the five situations in terms of the main outcomes of cost-effectiveness, including the aggregate financial costs, are listed in Table IV. The proportion of total direct costs for quetiapine was considerably higher in South Africa than in the UK. Therefore for private sector situations 1 and 2 quetiapine made up 14.2% and 13.9% of the total costs respectively, and for public sector situations 1 and 2 the figures were 16.5% and 16.2% respectively. (For private sector situations 1 and 2 haloperidol made up 1.7% and 1.7% of the total costs respectively, and for public sector situations 1 and 2 the figures were 2.1% and 2% respectively.)

The results of the sensitivity analysis (not reported here) showed that quetiapine remains less costly than haloperidol in almost all cases under the baseline and private 1 situation. In the case of situation public 1, where the cost differential was the smallest (R684 per patient over a 5-year period), changes in assumptions that saw treatment costs decline in almost all cases resulted in quetiapine patients being more costly to treat than haloperidol patients. Yet, the cost differential was relatively small where queti-

apine was not cost saving and ranged from R0.93 (assumed no relapse patients to be hospitalised compared with 60% in baseline situation) to R121.52 (assumed non-response and relapse health state costs to decline by 50% compared with public 1 situation) per patient per month.

The results of the conservative estimates (i.e. situation 1) for the private and public sectors are depicted graphically in Figs 1 and 2, respectively. It can be seen that over a 5-year period, while the acquisition costs of the two treatments differ substantially, the total direct costs are very similar.

Discussion

The results of our study show that, as in the UK, the direct costs are slightly less for quetiapine than for haloperidol for all of our situations in both the private and public sectors. Although the medication acquisition costs were higher for quetiapine, substantial savings were achieved by a reduction in the use of health care services. Cost savings per patient over 5 years amounted to

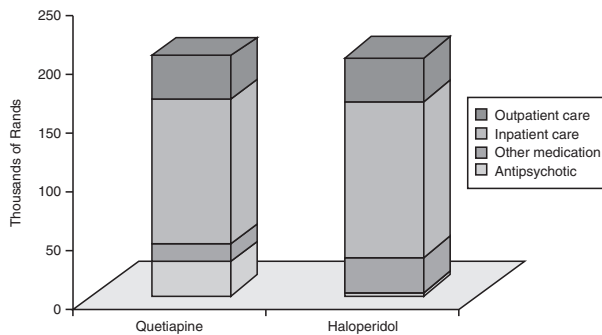


Fig. 1. Total estimated direct costs per patient treated in the private sector in South Africa.

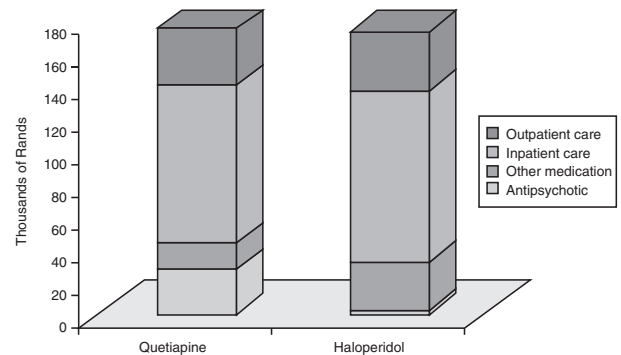


Fig. 2. Total estimated direct costs per patient treated in the public sector in South Africa.

Table IV. Estimated total costs of different health care situations for South Africa

Aggregate costs:	Baseline	Private 1	Private 2	Public 1	Public 2
Medical resource	Quetiapine	Quetiapine	Quetiapine	Quetiapine	Quetiapine
Total cost of study medication	28 939 380	29 152 857	29 429 104	29 152 857	29 429 104
Total cost of other medications	15 649 003	15 460 448	15 223 802	15 460 448	15 223 802
Total cost of inpatient services	117 528 542	124 027 492	129 995 166	97 955 878	103 218 503
Total cost of outpatient services	37 716 091	36 620 807	36 451 731	34 095 682	33 981 457
Total treatment costs	199 833 016	205 261 604	211 099 802	176 664 865	181 852 866
Medical resource	Haloperidol	Haloperidol	Haloperidol	Haloperidol	Haloperidol
Total cost of study medication	3 689 974	3 632 504	3 596 363	3 632 504	3 596 363
Total cost of other medications	30 884 712	31 130 841	31 312 363	31 130 841	31 312 363
Total cost of inpatient services	127 389 903	134 305 158	140 780 433	106 121 337	111 828 356
Total cost of outpatient services	40 508 846	39 251 527	39 035 591	36 465 297	36 312 806
Total treatment costs	202 473 435	208 320 030	214 724 750	177 349 978	183 049 888
Medical resource	Difference	Difference	Difference	Difference	Difference
Total cost of study medication	25 249 406	25 520 353	25 832 741	25 520 353	25 832 741
Total cost of other medications	-15 235 709	-15 670 393	-16 088 561	-15 670 393	-16 088 561
Total cost of inpatient services	-9 861 361	-10 277 666	-10 785 267	-8 165 459	-8 609 853
Total cost of outpatient services	-2 792 754	-2 630 721	-2 583 860	-2 369 615	-2 331 349
Total treatment costs	-2 640 419	-3 058 426	-3 624 947	-685 113	-1 197 022

R2 641 in the baseline situation, R3 058 and R3 625 in private situations 1 and 2, and R684 and R1 197 in public situations 1 and 2, respectively. However the cost differences are not great — for the private sector models they translate into a saving of R51 (private 1) or R60 per month (private 2) for quetiapine, and for the public sector models R11 (public 1) or R20 (public 2) per month.

We conducted our initial analysis using medication prices that were in effect before the recently introduced legislation that has resulted in significant cost cuts. In this analysis treatment with quetiapine did not result in cost savings compared with haloperidol. However, in view of the fact that recent legislation to introduce single exit prices has significantly cut costs of medication in South Africa,³¹ we decided to re-analyse the data using the prices introduced in August 2004. The new prices resulted in a reduction of 36.7% in the cost of quetiapine and 13% for haloperidol. As a result, quetiapine treatment is now 3.7 times more expensive than haloperidol treatment compared with the 5-fold difference in price assumed in our original model. The daily cost of the drugs used for atypical antipsychotics (15 mg olanzapine and 6 mg risperidone) increased marginally (1.3%), while the daily cost of anticholinergic treatment (4 mg akineton) declined by 7.5%. Consequently, the results of the cost-effectiveness analysis based on these new drug prices saw quetiapine patients being less costly to treat than haloperidol patients in all five situations. Although the cost of medication was higher for quetiapine, substantial cost savings were achieved by a reduction in the use of health care services. Cost saving over 5 years amounted to R2 889 in the baseline situation. Cost saving for private situations 1 and 2 amounted to R3 370 and R3 981, and R2 040 and R2 579 for public situations 1 and 2, respectively.

The analysis we used adopted a conservative approach, so that where data were not available, it was assumed that there were no differences between the treatments. This is unlikely to be the case, however, as improved side-effect profile³² and better patient acceptance³³ with quetiapine are likely to improve compliance and reduce the relapse rate and resource utilisation in the long term. Also, the model does not take some direct and all indirect costs into account. These latter costs are likely to be considerable. For example, only 12% of persons with schizophrenia were found to be employed in a full-time capacity in the USA,³⁴ and the illness is associated with poor physical health — patients with the illness are more likely to eat poorly and smoke and drink alcohol to excess, thus necessitating additional health-resource utilisation.³² Also, family members spend on average 1.5 hours per week³⁵

and an estimated \$3 500 per year³⁶ looking after a family member with schizophrenia.

Our findings cannot necessarily be generalised to other samples and need to be interpreted with caution because of a number of limitations. First, the entire model is based on indirect estimates in the absence of a prospective pharmaco-economic study. Second, the lack of good data on costs of care in both the private and public sector in South Africa make estimates difficult. The cost estimates employed in this study were derived from tariffs, which are unlikely to represent the true opportunity cost of resources in the absence of perfectly competitive markets³⁷ and may substantially underestimate the direct cost of treatment, thus possibly translating into greater cost savings than those reported here. Third, the inclusion in this analysis of the cost of suicide or attempted suicide (excluded here for the sake of simplicity and owing to absence of good estimates of the cost of suicide in South Africa), which is likely to be substantial,³⁸ may also have translated into considerable resource savings, resulting in quetiapine being even more cost saving. Fourth, relative costs of care differ substantially in developed and developing country settings. For example, comparative costs per bed day and outpatient visit compiled by the World Health Organisation (available at <http://www.who.int/evidence/cea>) show estimates for a country such as South Africa to represent one-quarter or less of the cost estimates for developed countries such as Canada, the USA and the UK.³⁹ More importantly, in terms of this study, it shows how higher relative costs are more likely to translate into cost-effectiveness, as noted by Drummond and Pang.⁴⁰ This emphasises how the relatively lower cost of health in a developing country such as South Africa is less likely to translate into cost effectiveness where the main cost savings result from the lower relapse rates and subsequent hospitalisation and resource use under the alternative treatment. Finally, considerable variation in intensity and nature of care exists in South Africa in both the private and public sectors.

Notwithstanding these limitations, as far as we are aware this study provides a first attempt at quantifying costs in treating schizophrenia in South Africa. Hopefully, it will focus attention on this often-neglected group of patients, and encourage further research in the area. We also hope that it will provide guidance to health care costing decision makers in both the private and public domains in South Africa. While costs ultimately play a large role in deciding what medications should be made available, other considerations are no less important. Particularly, from an ethical point of view it should be argued that every individual has the right to good medical care. There is now overwhelming evidence

of neurotoxic effects of haloperidol, so that even a traditionally conservative Cochrane meta-analysis recently concluded that 'given no choice of drug, use of haloperidol to counter the damaging and potentially dangerous consequences of untreated schizophrenia is justified. If a choice of drug is available, however, people with schizophrenia and clinicians may wish to start another antipsychotic with less likelihood of causing parkinsonism, akathisia and acute dystonias. For countries where haloperidol is not widely used, it should not be a control drug of choice for randomised trials of new antipsychotics.'⁴¹ This study provides economic support to add to the ethical argument for more extensive use of the atypical antipsychotics in treating schizophrenia in both the private and public sectors in South Africa.

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