ORIGINAL SCIENTIFIC PAPER

QUANTITATIVE RESEARCH

The impact on health outcome measures of switching to generic medicines consequent to reference pricing: the case of olanzapine in New Zealand

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ABSTRACT

INTRODUCTION: New Zealand's Pharmaceutical Management Agency (PHARMAC) manages the list of medicines available for prescribing with government subsidy, within a fixed annual medicines budget. PHARMAC achieves this through a mix of pricing strategies including reference pricing. In 2011, PHARMAC applied generic reference pricing to olanzapine tablets.

AIM: This study sought to evaluate change in outcome measures of patients switching from originator to generic olanzapine consequent to the introduction of the policy.

METHODS: A retrospective study using national health data collections was conducted. Outcome measures included medicines indicators (change in dosage, concomitant therapy and treatment cessation), health care service indicators (use of emergency departments, hospitals and specialist services), surveillance reports of adverse events, and mortality.

RESULTS: Subsequent to the removal of funding for originator brand olanzapine tablets, 99.7% of patients meeting the inclusion criteria switched to using generic olanzapine. Limited case reports of suspected therapeutic loss were received in the study time period. No increase in use of additional oral or injectable antipsychotic medication was observed after switching, nor any increase in other unique, non-antipsychotic prescription items. However, a high incidence of multiple switching between available brands was found. No net impact of switching brands on health service utilisation or mortality was found.

DISCUSSION: The study shows that a switch can be made safely from originator olanzapine to a generic brand, and suggests that switching to generics should generally be viewed more positively. Generic reference pricing achieves considerable savings and, as a pricing policy, could be applied more widely.

KEYWORDS: Antipsychotic agents; drug costs; drugs, generic; olanzapine

Introduction

The provision of medicines can consume a large proportion of a country's health care budget. In 2011, OECD countries spent an average of 16% of their total health expenditure on medicines, although there was wide variability in the proportion and actual amount spent per country.[1] Norway and Denmark spent the lowest at 7% of their total health expenditure on medicines, whilst Luxembourg, the Netherlands and Switzerland were similar to New Zealand's 9%. Some OECD countries, however, spend up to 30% of their health budget on medicines.[2]

One of the primary strategies used to minimise expenditure on medicines is reference pricing, whereby a single reference price is used as a benchmark for a group of medicines regarded as interchangeable and this becomes the maximum price paid for any medicine within the defined category. Generic reference pricing is employed by

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many countries and relies on the premise that generic versions of originator products are equivalent and interchangeable. This issue continues to be debated, despite 98% of some 2070 bioequivalence studies submitted to the FDA (US Food and Drug Administration) showing variations of less than 10% of that of their comparator originator brands.[3]

Olanzapine, an atypical antipsychotic medicine used in the management of schizophrenia and related psychoses, has been widely available internationally since 1996,[4] and in New Zealand (NZ) since 1999.[5] Until patent expiry in 2011, olanzapine was a relatively expensive medicine and in NZ singly accounted for more expenditure than any other medicine in 2010 (approximately NZ$30 million/year).[6]

New Zealand's Pharmaceutical Management Agency (PHARMAC) manages the list of medicines available for prescribing with government subsidy, within a fixed annual medicines budget. In June 2011, PHARMAC applied generic reference pricing to olanzapine, and listed two generic brands of olanzapine in the NZ Pharmaceutical Schedule for subsidy. The manufacturer of the originator Zyprexa brand did not reduce their price to meet the reference price and, in 2014, 28 x 10 mg tablets of Zyprexa were priced at NZ$200 (US$173), whilst the cost of generic olanzapine in NZ was less than 4% of the originator at NZ$6.00 (approximately US$5.20).[7,8] Funding for the originator brand Zyprexa was removed, with patients having to bear the full cost for this brand.

Large differences in the price of generic versus originator olanzapine similarly exist in most countries. For example, the British National Formulary reports that 28 tablets of 10 mg generic olanzapine costs £1.51 compared with £87.40 for the same amount of the originator brand.[9] Generic olanzapine (at 6% of the cost of originator) has been produced in Canada since 2009, but was the focus of litigation with the originator company until 2012.[10]

With large price differences between generic and originator drugs, there are clear incentives for health funders to prefer the less expensive generics. An issue consistently under debate is whether a switch can be made safely for patients, with the medicine's effectiveness maintained.[11–13] Opponents argue that such a policy restricts a medical practitioner's prescribing freedom, increases inequity in the health sector (as only those who can afford to pay for non-reference-priced drugs can access them), has negative health consequences, and increases use of other health services.[14,15] However, limited research evidence exists to address these arguments.

The NZ public has experienced brand switches since the mid-1990s; yet resistance to changes in the medicines listed in the Schedule persists.[12,13,16,17] A perception exists that certain medicines should not be substituted or that substitutions are more problematic amongst certain patients.[3] However, successful substitution with generic cyclosporin, long considered the archetypical non-interchangeable medicine, has been recently reported.[18] Further investigation into so-called 'problematic' medicines (such as those used to manage psychoses) is warranted in building the case for generic substitution. Few case reports exist of therapeutic failure where generic olanzapine has been used in place of the originator brand,[19–22] and only one small Polish study specifically examining olanzapine brand switches is available to date.[23] Specific, systematic information regarding the effect of switching from originator olanzapine to generic olanzapine is lacking.

This NZ retrospective study sought to inform the debate about generic reference pricing policies, using certain health care indicators available in national databases to evaluate the impact

WHAT GAP THIS FILLS

What we already know: Prices for generic medicines are lower than originator branded medicines, with health funders preferring generics over originator brands where possible. Uncertainty surrounds the clinical equivalence of generic medicines and the effect of brand substitution on health outcomes.

What this study adds: Evidence is provided, in the New Zealand setting, of a lack of negative consequences of olanzapine brand switching. Brand switching in general could be applied more widely; however, the reasons for multiple switches between available generic brands should be explored.

on health outcomes for patients switching from originator brand olanzapine to generic olanzapine.

Methods

Using the national pharmaceutical claims database (PHARMS), a retrospective study was undertaken of all adult patients (aged 14 years or older) in NZ who had been dispensed olanzapine tablets at least five times during the six months prior to the introduction of generic olanzapine (1 June 2011) and also for the six-month period prior to 1 June 2010 (i.e. one year earlier). From this group, patients who switched to generic olanzapine from Zyprexa following the withdrawal of subsidy payments for Zyprexa on 1 September 2011 (i.e. the 'intervention') were identified. Individual 'switch dates' (the date of the intervention) were noted and the time taken to switch was calculated from 1 September 2011, this being the date of change in subsidy for the originator brand.

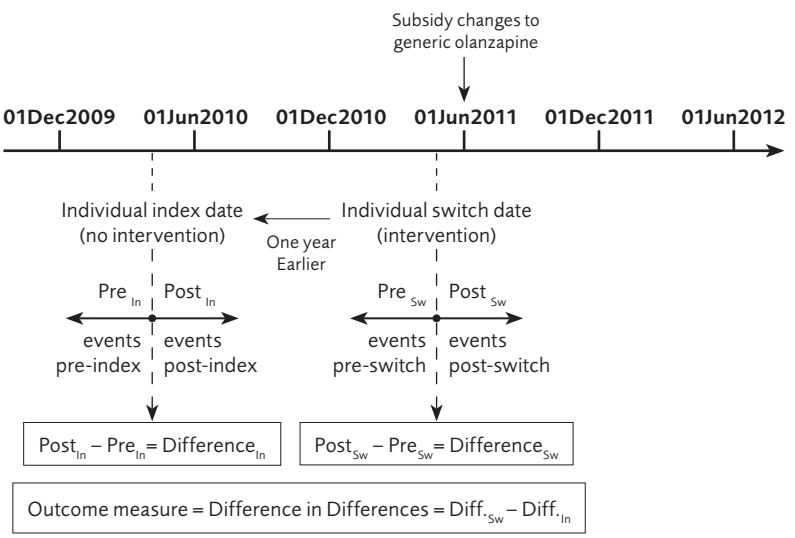
Likewise 'non-switchers' were also identified, with the intention of comparing switchers with non-switchers; however, only 16 patients did not switch to generic olanzapine and were excluded from the study, being too small a cohort to use as a control group. Instead, outcomes were evaluated for the switchers, during an earlier no-intervention period. An 'index date' was computed for each patient, being one year earlier than their switch date, in order that comparison could be made between intervention and no-intervention periods, with patients acting as their own controls.

Prescription records were used to compute an unweighted chronic disease score using the World Health Organization's Anatomical Therapeutic Chemical classification system for all unique chronic medicines (excluding antipsychotic medicines) dispensed to each patient.[24] Prescription records were further used to identify any change in the number of antipsychotic medicines (both oral and injectable) used per patient, and any change in dose of olanzapine or cessation of therapy. The number of unique prescription items was also identified for each period.

Medical encounters as events were identified from national data collections linked via an encrypted unique patient identifier, the National Health Index (NHI) number,[25] and comprised unplanned visits to a hospital (either to the emergency department [ED] or admission as an inpatient), and referrals to outpatient specialist clinics. Events were counted at two time-points (30 and 180 days) for both the pre- and post-intervention and for the no-intervention periods (See Figure 1). The national deaths register was examined for one year following the switch date to identify deaths amongst study participants.

As data were collected at an individual patient level, paired tests of significance were conducted where appropriate, with *p*-values of less than 0.05 taken as significant. For each patient, the difference in the number of events post- minus pre- intervention and for the no-intervention period were calculated, giving individualised changes in the rate of utilisation of that health service. Mean differences in the outcome variables between the intervention (switch) period were compared with the no-intervention period one year earlier, with the differences in these changes (difference-in-differences) examined (see Figure 1).

Figure 1. Schematic representation of determination of outcome measures



Notes: Generic reference pricing was instituted on 1st June 2011. Switch dates were determined for each of the 5223 included patients, and an 'Index date' was assigned to each patient, being one year earlier. The number of events for each outcome measure was determined pre- and post-index date and pre- and post-switch date, allowing the outcome 'difference in differences' to be calculated.

Baseline demographics including age, gender, index of deprivation of domicile and comorbidity measures were used as explanatory variables, and correlations with switch status examined. Data were managed and statistical analyses conducted using Microsoft® Excel and SPSS version 21. This study was approved by The University of Auckland Human Ethics committee and the Ministry of Health of NZ.

Results

Demographics and switching pattern

A description of the study population is given in Table 1. The majority of all patients (98.2%) had switched within three months of implementation of the pricing policy, with a further 1.5% switching within 12 months. As a large proportion had switched ahead of the policy date of 1 September 2011, the mean time to switch was negative 22 days (standard deviation [SD] = 53.5 days).

In the one-year follow-up, 12.5% of study patients made a single switch, whilst 86% switched from the originator brand to a generic and then made a further switch to a second generic brand. A small percentage of patients (1.4%) switched from originator to generic, back to originator and then to generic again.

Table 1. Baseline demographic characteristics of olanzapine cohort

Demographic	Finding (N=5223)
Mean age	53.2 years
Aged ≥65 years	22.7%
Aged ≥80 years	7.1%
Female	46.3%
New Zealand European	70.4%
Māori and Pacific	22.1%
Proportion living in area of most deprivation (NZDep* of 7–10)	56.5%
Proportion with no additional comorbidity	21.4%
Comorbidities of 3 or more	35.8%
Study medicine as monotherapy	71.2%

* The New Zealand Deprivation Index (NZDep) 2001 is a 10-point scale, with an index of 10 indicating the area of domicile is lived in by the least socially and materially well-off people, which is widely used in health research.

Medicine indicators

Change in use of antipsychotic medicines

For 71% of patients, the only antipsychotic medicine received was olanzapine. The small increase in six-month use of additional oral antipsychotics post-switching (0.02) was less than the increase observed during the same six-month period one year earlier (0.12), with the mean use of additional oral antipsychotic medicines per person decreasing over the entire study time period (-0.1/person; $p<0.001$).

Most of the study patients (94.8%) did not receive any injectable antipsychotic medicines throughout the study period. No significant change in use of injectable antipsychotic medicines six months after switching was found for the 273 patients who had received injections in the six months prior to the switch. Comparing the post–pre intervention difference around the switch date with the same six-month period from one year earlier, fewer injections were used in these same patients post-switching; (difference in differences = -0.92; $p<0.001$; see Table 2).

Change in dose

Complete dosage information was available for 2211 patients over the study period (42% of the study group). A mean dose of 12.28 mg (SD 9.1 mg) was found for these patients pre-switching. For the majority of these patients (95%), no change in total daily dose was observed six months post-switching (mean dose post-switch = 12.20 mg; SD 9.1 mg). However, dosage information was incomplete for the remaining 58% of the study cohort.

Cessation of olanzapine therapy

Fifty-two patients (1%) did not receive any further dispensings of olanzapine after switching and a further 31 patients only received one further prescription after switching. The proportion of patients discontinuing olanzapine within eight weeks of switching was therefore 1.6% in total.

Change in number of unique prescription items

A significant but small decrease in the number of unique prescription items was found during the

Table 2. Summary of medicine indicators

Indicator (N=5223 unless otherwise stated)	Finding
Time to switch (days)	-22 days (range -92 to >365 days)
Proportion making a single switch	12.5%
Proportion with no dose change (180 days); n=2211	95%
Proportion stopping olanzapine therapy (180 days)	1.6%
Change in oral antipsychotic add-on therapy (180 days)	-0.10*; $p<0.001$
Change in use of antipsychotic injection (180 days); n=273	-0.92*; $p<0.001$
Change in unique prescription count (365 days)	-0.41*; $p<0.001$

* i.e. patients used less in the year following switching than the preceding year

intervention (post-switch) year compared with the no-intervention year (-0.41; $p<0.001$).

Adverse reaction reporting

Between 2008 and 2013, 110 reports relating to olanzapine were received by the national pharmacovigilance centre (Centre for Adverse Reactions Monitoring [CARM]). During the study years 2011–2012, CARM received 38 reports related to olanzapine, 12 of which involved switching brands. A reduced therapeutic response was suspected in four cases, with the balance of reports being for unspecified adverse reactions.[26]

Health care indicators

No significant difference in the use of any of the measured health services (ED, specialist outpatient services and admissions to hospital) was found at either 30 days or 180 days post-switching when compared with the same time period one year earlier (see Table 3). No correlation was found between patients making multiple switches and utilisation of health services.

Mortality

There were 41 deaths amongst the 5223 study patients (rate of 0.008) in the three months following brand switching, with the mean age of these patients being 71.5 years (median 77.3 years). No deaths recorded medication issues as the primary or secondary cause of death, with 11 deaths subject to coroner's findings at the time of the study. Of the entire study cohort, 144 patients had died within one year of switching (rate of 0.028), in line with the death rate found for people with

Table 3. Summary of health care indicators (N=5223)

Health service used	Change* in use of health service on switching to a generic brand; intervention	Change* in use of health service one year before switching, patients taking the originator brand; no intervention	Difference in differences (95% CI); p-value
Emergency Department at 30 days	0.024	-0.003	0.027 (-0.01 to 0.06); 0.16
Specialist outpatient at 30 days	-0.011	-0.015	0.004 (-0.03 to 0.04); 0.82
Specialist outpatient at 180 days	-0.056	0.023	-0.079 (-0.25 to 0.09); 0.35
Hospitalisations at 30 days	0.005	-0.002	0.007 (-0.003 to 0.02); 0.18
Hospitalisations at 180 days	0.013	-0.013	0.026 (-0.001 to 0.05); 0.06

* Difference between post- and pre-intervention period

a diagnosis of a psychotic disorder in NZ (being three times the national death rate of 0.008 for adults in 2011).[27,28]

Discussion

Impact of switching

This study found no increase in hospitalisations, use of ED or specialist outpatient services, or untoward health events in patients following switching from Zyprexa to generic olanzapine. No changes in dosage and no increase in the mean use of additional oral or injectable antipsychotic medicines per person were found. The rate of spontaneous adverse event reporting was similar to the rate of reports to CARM for risperidone during the same 2008–2013 period. The rate of death following switching was not significantly different from death rates reported for New Zealanders with a diagnosis of a psychotic disorder,[28] or from adult users of risperidone in NZ.[29]

Reviews that evaluate generic psychotropic medicines and the issue of switching are available in the literature; however, reports that extrapolate the effects of typical antipsychotics against the pharmacologically different atypical ones should be met with caution.[30,31] Little evidence is available for the relatively newer atypical antipsychotic medicines, such as olanzapine, and few published reports of olanzapine bioequivalence studies exist, aside from those conducted for product registration.[32] Very few case reports of adverse events related to changing between brands of olanzapine exist in the literature,[20–23] despite around 100 pharmaceutical companies selling generic olanzapine throughout the world.[33]

With limited information available in the literature and a lack of head-to-head clinical trials between different olanzapine brands, observational studies such as this one using national datasets provide the best available evidence for equivalence of generic and originator brand medicines.[34,35]

Switching behaviour

Notably, the majority of patients (86%) made multiple switches between available generic brands. This may be incidental switching within or between community pharmacies or public hospital, or it might be a consequence of different generic brands being used between levels of care. For example, in 2014 there were two generic brands of olanzapine on the Hospital Medicines List and three brands available within the community sector. PHARMAC initially only managed the Community Pharmaceutical Schedule, but in 2010 was tasked with managing hospital medicines, which should see a closer alignment of medicine lists between hospital and community-based care and reduce the impact of patient movement through the health sector on switching between different generic brands. The impact of making multiple switches is unclear. Beliefs about medication are regarded as an important predictor of non-adherence to treatment, which in turn is associated with readmissions and increased health care costs.[36–38] There is little literature quantifying the specific impact of switching on adherence, and none on the impact of multiple switches. However, given that suspicion is a feature of the illness for which olanzapine is prescribed and trust a prerequisite to successful therapy, changes in appearance (colour, size, and packaging) to a medicine has the potential to increase non-adherence and increase costs.[39] Although multiple switching within short periods of time is probably undesirable, this study found no correlation between multiple switches and health care outcomes.

Policy implications

Of the more than 5000 patients consistently using olanzapine medication in NZ during the time of this study, only 16 patients did not switch to generic olanzapine following the withdrawal of subsidy payments for the originator brand of olanzapine tablets on 1 September 2011. A rapid and almost complete switch to generic olanzapine, with no net adverse health outcomes, reflects the desired outcome of NZ's policy of generic reference-pricing in savings made to the annual community pharmaceutical budget.

At the average dose of olanzapine received by patients in this study of 12.5 mg (nearest tablet size to 12.28 mg), a year's supply of originator olanzapine would cost NZ$3,322.28 at the

time of writing, whilst that of the generic costs NZ$108.55. The savings over a year for the patients in this study alone amounts to NZ$16 million (NZ$16,611,400.00 for originator versus NZ$542,750.00 for generic olanzapine).[40]

The study suggests that a switch can be made safely from originator olanzapine to one of the available generic brands. No increase in the use of health care services as a consequence of switching could be found in the NZ setting. More widely, this study adds to the argument for the use of generics once originator brands have come off patent, as a means of making large savings to pharmaceutical budgets. It supports the use of reference pricing as a policy and shows how national health datasets can be used to validate policy decisions.

Limitations

Limitations of this study are acknowledged, including the potential for bias introduced by a lack of randomisation, no control over the exposure of interest, misclassification in or incompleteness of the data, confounding that cannot be measured within the databases, or the influence of external factors. The strength, however, of using an observational study such as this is that it presents the lived experience of patients under the influence of a nationally implemented pricing policy, which a randomised clinical trial cannot offer. Ideally, the availability of a comparator group of olanzapine non-switchers would have made the findings more robust. However, this evaluation includes the post–pre differences in measures one year earlier for each patient, using the switcher patients as their own non-switcher controls, and in doing so also eliminates between-group confounders.

In using national datasets to determine events, those events that are self-managed by the patient will not be accounted for. Additionally, any change in the use of the general practitioner (GP), or of the network of the community mental health team, case managers and other support workers could not be measured in this study as the data were not captured within a national dataset during this time.

Ad hoc or rescue use of injectable antipsychotic medicines within the GP practice is most often not recorded in the PHARMS database on a named patient basis, and thus will be missing from the data. It is also noted that, although the dispensing of a medicine does not equate to actual use, information collected in pharmacy databases is generally recognised as a reasonable approximation of medicine use.[35]

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