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An Evaluation of Health Service Impacts Consequent to Switching from Brand to Generic Venlafaxine in New Zealand under Conditions of Price Neutrality

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ABSTRACT

Objective: To study the health impact on adult New Zealand patients who switch from originator brand to generic venlafaxine. **Methods:** The national pharmacy database was used to select patients using venlafaxine for at least 6 months. Switchers and nonswitchers were identified, and switch behavior was compared for a 12-month follow-up period. Change in health service use following switching was also compared between switchers and nonswitchers including use of the emergency department, hospital, and specialist outpatient services over the same period. **Results:** Approximately 12% of all originator brand users switched to generic venlafaxine, at least half of whom continued to use the generic throughout the follow-up period to August 1, 2012. Almost 60% of new users of the generic venlafaxine, however, switched to using the originator brand. Aside from a slight reduction in the use of outpatient services among switchers, there were no significant differences in health services use between switchers and nonswitchers for either existing or new venlafaxine users. **Conclusions:** Although both products remain fully subsidized and available, there is little incentive for prescribers, pharmacists, or patients to switch to the less expensive generic brand. If savings to the national New Zealand budget are to be realized, additional policy measures should be implemented to minimize incentives for multiple and reverse switching, and prescribers, as key opinion leaders, could take the lead in promoting generics to their patients.

Keywords: generic, pharmaceutical pricing, substitution, venlafaxine.

Introduction

Depression affects more than 130 million people worldwide, with an estimated lifetime prevalence of 10% to 15%. It carries a burden of illness in itself and has been associated with greater rates of mortality following myocardial infarction and stroke, and 20-fold increases in the rate of death from suicide [1]. In addition, decreased workplace productivity and psychosocial disability are key features of depression [1]. The World Health Organization suggests that by 2030 depression will be the leading cause of disease burden, with the disease affecting both developed and developing countries [1,2].

The lifetime risk for a major depressive illness in New Zealand has been estimated to be approximately 25%, with a median age of onset occurring in the early 1930s. It is expected that one in four adults will experience an episode of major depression in his or her lifetime [3]. Alongside psychosocial therapy, antidepressant medicines form the mainstay of treatment, with selective serotonin reuptake inhibitors (SSRIs) usually being the first choice of antidepressants. The advent of venlafaxine—a serotonin-noradrenaline reuptake inhibitor—in the late 1990s offered an additional treatment option in the antidepressant armory alongside related SSRIs, despite higher rates of adverse events [4].

In New Zealand, the use of venlafaxine has generally been reserved for "treatment-resistant" depression when a trial of at least two other antidepressant medicines has not been successful [5,6]. The originator brand Efexor-XR was introduced in the New Zealand market and subsidized by the government in early 2004, with special restrictions requiring prescriptions to be initiated only by a psychiatrist to limit usage while increasing experience with the medicine. In 2007, access was widened to include psychiatric registrars and vocationally registered general practitioners and usage of the medicine increased. In mid-2011, a less expensive generic version of venlafaxine (Arrow Venlafaxine XR) became available, subject to the same prescribing and subsidy conditions as the originator brand [7]. No incentive, however, was given to pharmacists or prescribers to encourage their patients to switch to the generic. Indeed, a reverse incentive remains in place for pharmacists to both commence new patients and continue existing ones on the more expensive originator brand because the pharmacy fee is made up in part of a percentage of the base cost of the medicine.

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The clinical justification for switching between brands of the same pharmaceutical preparation rests on an assumption of bioequivalence, that is, both medicines' overall bioavailability and maximum plasma concentrations being the same [8]. A limited number of medicines are traditionally considered noninterchangeable, either when bioequivalence has not been established or the therapeutic index is narrow and the risk of toxicity high. Despite this, successful substitution with generic cyclosporine, long considered the archetypical noninterchangeable medicine, has been recently reported in heart transplant patients [9]. Establishing bioequivalence, however, does not guarantee acceptance of the "same-but-different" generic medicine by health professionals or patients, and concerns linger around the interchangeability of generic medicines with their originator counterparts [10,11]. Literature related to brand switching of SSRI and serotonin-noradrenaline reuptake inhibitor medicines focuses mainly on the market share of the brands, especially in insurance settings with tiered-pricing plans that favor generic equivalents for full subsidy [12]. Studies evaluating health outcomes of SSRI brand switching are limited in number and methodology. A US-based study reported increased health care costs associated with therapeutic brand switching (changing from one chemical entity to another), yet reported on brand-to-generic switching of SSRIs as a whole. The switcher patients included in this study also had significantly different baseline scores for depression than did their matched nonswitcher counterparts [13]. Available reviews of brand-to-generic switching of psychotropic medicines include literature on a diverse range of medicines including older and newer antidepressives, antipsychotics, and antiepileptic medicines, blurring the picture on these distinct pharmacological entities and contributing to misperceptions [14,15].

New Zealand's Pharmaceutical Management Agency (PHARMAC) is the agency responsible for making funding decisions regarding which pharmaceutical preparations will be listed in the Pharmaceutical Schedule and thus provided largely free to all New Zealanders (outside of a co-payment of $5). Within a fixed annual budget, PHARMAC purchases around 2000 prescription preparations. Evidence-based appraisals are used by PHARMAC in funding decisions for novel medicines, as they are in similar agencies in England, Canada, and Australia. In making funding decisions on generic medicines, however, PHARMAC and its sister agencies must rely on bioequivalence studies as submitted with product registration.

Although the bioequivalence and substitution of some medicines, for example, of originator brand aspirin with generic aspirin, has long been accepted, substitution of medicines for chronic illnesses with generic equivalents is viewed with suspicion by patients as well as by pharmacists and doctors [16,17]. With the availability of a generic brand of venlafaxine in New Zealand, PHARMAC has included both generic and originator brand in the Schedule, rather than adopting a more stringent funding decision that might have seen only generic venlafaxine fully subsidized and the originator brand partially or unsubsidized. Over time, use of the generic brand would be expected to increase through the use of venlafaxine by new patients as well as through incidental switching from originator to the generic brand (known to occur for risperidone, olanzapine, and quetiapine at least) [18].

It is the patients using the generic option in a setting of price neutrality who offer an opportunity to evaluate the consequences of venlafaxine brand switching, with the aim of identifying opportunities or risks of brand switching within the New Zealand context.

Methods

A retrospective study using the national health and pharmacy claims data sets was undertaken of all adult patients in New Zealand using venlafaxine during the period from February 1, 2011, to August 1, 2013.

Data Sources

Prescription records are kept in a centralized government database, the "PHARMS data set," and form the basis for reimbursement to pharmacies for the dispensing of prescription medicines and service provision. In addition, all contacts with the public health sector made by a patient are documented within a number of other databases held by the Ministry of Health. The National Minimum Dataset is a national collection of public and private hospital discharge information, including coded clinical data for inpatients and day patients, whereas the National Non-Admitted Patients Collection information includes event-based purchase units of medical and surgical outpatient events and visits to the emergency department (ED). The Mortality Collection records the underlying cause of death for all deaths registered in New Zealand. Linkage of these data sets via an encrypted National Health Index has been validated and is the basis of many New Zealand health services studies [19].

Patients' demographic characteristics that were extracted include age, sex, ethnicity, and home address. An individual's home address is further associated with a place of domicile index —the New Zealand small-area index of relative socioeconomic deprivation ("NZDep"), which is derived from census data. The NZDep 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. It is widely used in health research as well as by planners and for the allocation of health funds in New Zealand [20], and was also extracted for inclusion in the analysis.

Information on the cost and availability of venlafaxine was sourced from publicly accessible information from PHARMAC Annual Reports and the Pharmaceutical Schedule. Adverse reaction reports were obtained from the national Centre for Adverse Reactions Monitoring (CARM).

Cohorts

On August 1, 2011, generic venlafaxine became available for prescribing with full subsidy, although advance notice of its availability had been given to prescribers and pharmacies for at least 6 months (to allow for a period of stabilization of both drug choice and dosage) and in keeping with New Zealand guidelines [6]. Thus, from this date onward, it was anticipated that there would be new users of both the originator and the generic brands as well as existing users of the originator brand. Accordingly, study cohorts were constructed using the pharmacy data set to identify both new users of venlafaxine (either brand) and patients using originator venlafaxine continuously for at least 6 months before the introduction of the generic on August 1, 2011 (see Fig. 1). Adult patients who received a continuous supply of originator venlafaxine (prescriptions dispensed covering at least 168 days) in the 6 months preceding August 1, 2011, formed the "existing user" cohort (n = 10,212). Two further cohorts were constructed from patients using venlafaxine for the first time between August 1, 2011, and July 31, 2012, and for 6 successive months: one of new users of the originator venlafaxine (n = 3819) and another for the generic venlafaxine (n = 201).

Switch dates were recorded for all switchers and the time taken to switch calculated (days), this being the difference from the start date in the case of new users and from the policy date of August 1, 2011, in the case of existing users. Nonswitcher patients were assigned an "index date" upon which outcomes preindex and postindex date could be measured. Assigned index dates proportionally matched switch dates of switchers, and were randomly allocated. Follow-up was conducted for a period of 12

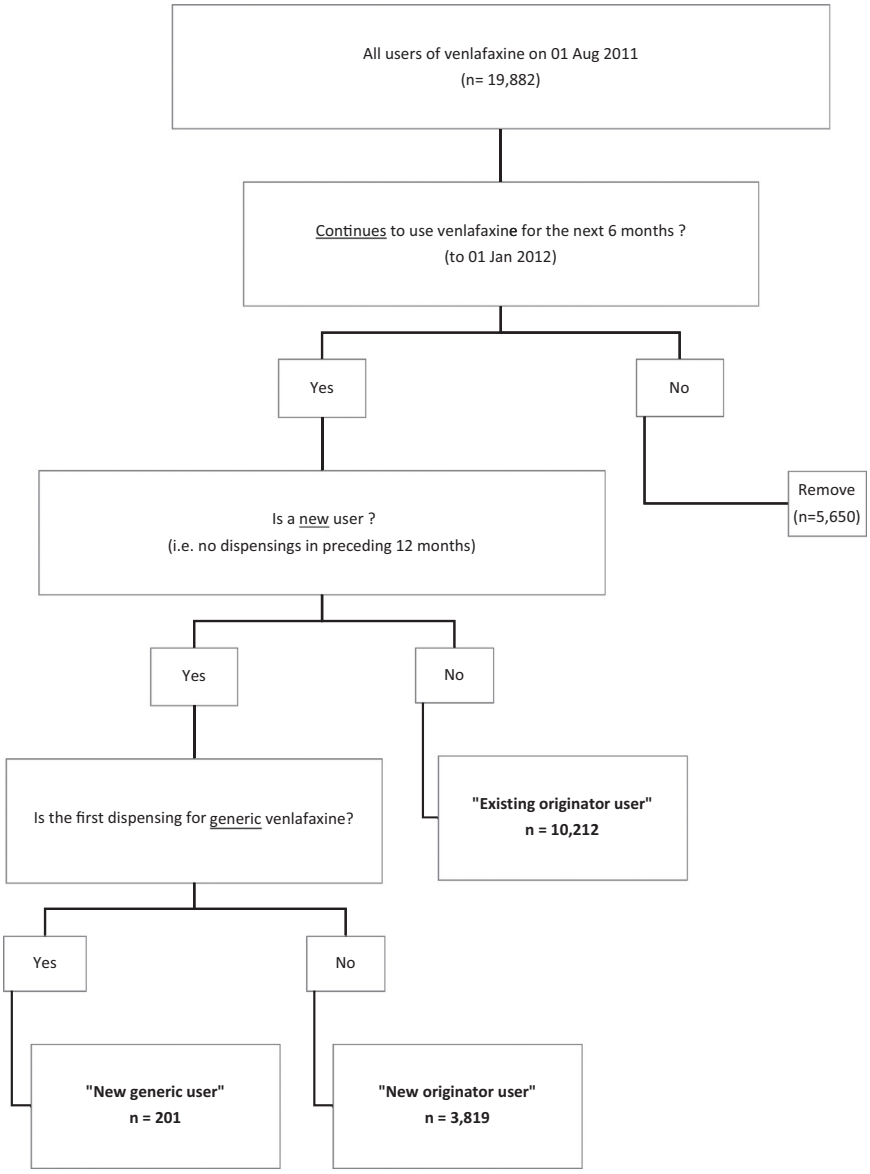

Fig. 1 – Construction of venlafaxine study cohorts.

months postswitch (for switchers) or postindex (for nonswitchers) in the existing user cohort, and for 6 months in the new user groups. The number of switches was counted for each patient, and specifically the rate of switching back to a previous brand within 14 days—a "switch-back"—was noted.

Data Management and Analysis

Baseline characteristics were examined for any statistical differences using *t* tests for continuous data and chi-square test for categorical data where appropriate. Prescription records were used to identify baseline comorbidities, as well as any change in the number of antidepressant medicines used per patient. Different disease score methods have been described; however, no "criterion standard" has yet been agreed on [21–23]. Most use *International Classification of Diseases, Ninth Revision* or other diagnostic codes, whereas a few use medications as the primary source of information, the so-called chronic disease score, wherein prescribed medicines are associated with disease groups and used to inform costs or outcomes—with or without additional weighting for the relative severity of disease [24–28]. This study used an unweighted chronic disease score, using the World Health Organization's "Anatomical Therapeutic Chemical Classification System," to assess all unique chronic medicines (excluding depression) dispensed to each patient. In addition, a simplified score of the number of distinct prescription medicines in the year preceding the index date was used because this has been suggested to be as effective in predicting future health care utilization as using a weighted chronic disease score [29,30]. Correlation with switch status was examined for demographic variables.

Medical encounters were identified from national data collections and included unplanned visits to a hospital (either to the ED or admission as an inpatient) and referrals to outpatient specialist clinics. Health outcome variables are presented as counts/person (e.g., number of visits to the ED per person per time period). In addition, a composite outcome of all visits (i.e., number of visits to ED + inpatient + outpatient per person per time period) was computed. Because data were collected at an individual patient level, paired tests of significance were

conducted where relevant, with P values of less than 0.05 taken as significant. Differences in the number of health events for both the preindex and postindex periods were used to determine the change in rate of utilization, with 95% confidence limits presented for each outcome. Difference-in-differences values are presented for the outcomes in switchers versus nonswitchers.

Adverse reaction data were obtained from the national CARM. The national deaths register was also examined for 1 year following the index or switch date to identify any of the study participants.

Data were managed and statistical analyses conducted using Microsoft Excel (Microsoft Corporation, Redmond, WA) and SPSS (version 18; IBM Software New York, NY). This study was approved by the University of Auckland Human Ethics Committee, and permission to access patient data was received from the Ministry of Health of New Zealand.

Results

Demographic characteristics of the Cohorts

In the first 6 months following the introduction of generic venlafaxine in the PHARMAC Schedule, uptake of the generic brand was low, with only 201 new generic users (5%) meeting the inclusion criteria compared with 3819 new users of originator venlafaxine. (Note that this does not necessarily reflect all users of venlafaxine in New Zealand, rather only those for whom a continuous 6-month supply could be identified from the PHARMS database.) Table 1 presents the characteristics of the cohorts, and Table 2 presents the characteristics of switchers and nonswitchers.

Nonswitchers were slightly older than switchers in both new user cohorts, whereas a higher proportion of switchers lived in areas of greater deprivation (NZDep 7–10). For new users of generic venlafaxine, the apparent difference in deprivation index did not reach statistical significance, possibly because of the small size of the group. Venlafaxine was used as monotherapy slightly less in existing nonswitcher users than in switchers, but equally in the new user cohorts.

The correlation of demographic factors with switch status was examined; however, individual correlations were weak, with the variables only minimally accounting for the likelihood to switch. Regression analysis revealed a Nagelkerke R^2 of 0.008 for the predictors of demographic characteristics and monotherapy and comorbidity (i.e., the predictors accounted for <1% of variance.) Monotherapy was the only predictor indicating likelihood to switch (odds ratio 0.80 for not switching [95% confidence interval 0.69–0.92]).

Table 1 – Key demographic characteristics of the three venlafaxine cohorts*.

Characteristic	Existing originator users	New originator users	New generic users
Number	10,212	3819	201
Sex: male (%)	35	36	41
European (%)	88	86	86
Maori and Pacifica (%)	6	7	7
Living in area of high socioeconomic deprivation (%)	41	41	43
Mean age (y)	49	45	44

* Existing originator users had been using originator brand venlafaxine for at least 6 mo before the policy date (August 1, 2011), whereas new users had not been exposed to venlafaxine (either brand) before that date.

Switching Patterns

Switching between available brands was noted for a period of up to 1 year from August 1, 2011. Of the 10,212 existing originator brand users, most of the patients continued using the originator brand ("nonswitchers"), with only 12% switching to the generic (see Table 3). Similarly, most of the new originator brand users (88%) did not switch. Conversely, a large proportion (almost 60%) of the generic new users made at least one brand switch.

Prescriptions for venlafaxine are generally written for a 3-month period, usually in 1-month lots. The time to make the first switch was similar for both originator brand user cohorts, with a switch first occurring around 6 months from August 1, 2011. New generic users switched slightly earlier on average at 4 months from commencement.

In both originator brand switcher groups, more than half made a single switch; that is, they switched to generic venlafaxine and continued using it throughout the following year (see Table 3). Forty-five of the switchers (3.8%) from the existing user group, however, made a switch back to originator venlafaxine within 14 days of their first switch.

Twenty-four percent of existing switchers and 36% of new originator brand switchers returned to using the previously used brand (generic-to-originator). Among the new generic user switchers, most (71%) switched from generic to originator brand. Among all switchers, more than 1 in 10 patients made multiple ($\geq$3) switches.

Pharmacy and Prescriber Loyalty

Most patients included in this study used a single prescriber (range 93%–97%). Among all switchers combined (n = 1742), 79% used a single pharmacy, compared with 94% of nonswitchers. A statistically significant but weak correlation exists between switching and number of pharmacies used ($P = 0.000$; Pearson $r = 0.14$). The maximum number of pharmacies used by a single patient was 13.

In addition, 30% of all pharmacies never dispensed generic venlafaxine between August 1, 2011, when it became available, and January 31, 2014.

Health Outcomes

The findings observed for existing originator brand users are summarized in Table 4 and for new users in Table 5. There were too few new users of generic venlafaxine to detect differences between switchers and nonswitchers and hence the findings are not presented.

Health services use

For existing originator users, there were no significant differences between switchers and nonswitchers in all outcome measures except the lower use of specialist outpatient services over 1 year made by switchers (0.6 less visits/person). No differences in health services use between switcher and nonswitcher new originator users were found. For all contacts made with the health system combined (composite outcome of ED use, hospitalizations, and outpatient specialist services), no difference could be found between switchers and nonswitchers at 6 months, for either new or for existing users of the originator brand.

Table 2 – Key demographic characteristics of switchers vs. nonswitchers by cohort*.

Characteristic	Existing originator users		New originator users		New generic users	
	Nonswitcher (n = 9036)	Switcher (n = 1176)	Nonswitcher (n = 3371)	Switcher (n = 448)	Nonswitcher (n = 83)	Switcher (n = 118)
Proportion (%)	88.5	11.5	88.3	11.7	41.3	58.7
Sex: male (%)	34.6	37.3	36.3	35.0	38.6	42.4
European (%)	87.7	87.7	85.9	84.2	83.1	87.3
Maori and Pacific peoples (%)	6.0	6.7	6.9	8.5	7.2	5.9
Living in area of high socioeconomic deprivation (%)	40.4	42.3	39.7† ($P = 0.007$; $r = 0.04$)	46.2	36.1	47.0
Mean age (y)	48.9	48.4	45.2† ($P = 0.001$; $r = -0.05$)	42.9	46.8† ($P = 0.012$; $r = -0.18$)	41.3
Median comorbidity count	2	2	1	1	1	1
Venlafaxine as monotherapy (%)	67.5† ($P = 0.001$; $r = 0.03$)	72.5	74.9	73.9	81.9	73.7

* Existing originator users had been using originator brand venlafaxine for at least 6 mo before the policy date (August 1, 2011), whereas new users had not been exposed to venlafaxine (either brand) before that date.
† Significant vs. switcher. A switcher is a patient changing from one brand to a second brand (either originator-to-generic or generic-to-originator). Nonswitchers did not make a change in brand.

Reports to CARM

New Zealand's national CARM receives reports from doctors, pharmacists, patients, and the pharmaceutical industry. Before the introduction of generic venlafaxine, on average 35 reports were received by CARM annually for originator venlafaxine. During the year 2011 immediately following the introduction of generic venlafaxine, no reports of adverse events were received related to a change in brand, whereas there were 33 other adverse events reported related to venlafaxine in general. In 2012, of the 29 reports received, 4 related to a brand switch, and in 2013, 2 out of 16 reports were brand-switch related. None of the switch-related reports, however, was for loss in therapeutic response.

Deaths

The rate of death among existing originator users was the same for nonswitchers (0.02) and switchers (0.02) when followed up for at least 1 year after the index date. For new users of originator venlafaxine, the rates were 0.01 and 0.004 for nonswitchers and switchers, respectively, and for new generic brand users was 0.01 for both nonswitchers and switchers.

Discussion

Uptake of generic venlafaxine among new users in New Zealand is low at 5%, and minimal switching to the generic occurs. Approximately 12% of the 14,031 originator brand users in this study switched to generic venlafaxine, whereas approximately 60% of the 201 generic users switched to the originator brand (i.e., "reverse switching"). No net effect on health service use, however, could be found for either new or existing originator-to-generic brand switcher patients compared with nonswitchers.

Some 4% of the patients switched back to the originator brand within 2 weeks of switching, suggesting a possible adverse response to the generic brand. Despite being unable to provide a precise reason for a switch-back, such a rate is of the order expected with any medicine that may equally be due to the excipients in the formulation, and no reports of loss in therapeutic effect were received by the adverse reactions monitoring center, CARM, during the study years.

The findings of this study are consistent with those of similar studies from New Zealand evaluating the effects of lamotrigine and risperidone brand switching where, despite patterns of multiple switches among patients, no adverse effects were evident [31,32]. Further reports related to venlafaxine include a report of therapeutic drug monitoring of venlafaxine in Germany among 35 patients that found no difference in serum concentrations between originator brand and generic formulations [33], and another bioavailability study among volunteers where no difference between originator and generic formulations was found [34]. Another study determined that the maximum plasma concentration between different venlafaxine preparations was initially (up to 6 hours) not the same, yet at steady state, no

Table 3 – Switching patterns of the three venlafaxine cohorts*.

Measure	Existing originator users	New originator users	New generic users
Number of switchers (proportion)	1172 (11.5%)	448 (11.7%)	118 (58.7%)
Days to first switch, mean ± SD	189 ± 129	175 ± 110	121 ± 98
Number (%) making a single switch	712 (60)	230 (51)	84 (71)
Proportion switching back within 14 d	45 (3.8%)	1 (0.2%)	0
Number (%) making a second switch†	290 (24)	163 (36)	16 (14)
Number (%) making ≥3 switches†	129 (11)	54 (12)	18 (15)

* Existing originator users had been using originator brand venlafaxine for at least 6 mo before the policy date (August 1, 2011), whereas new users had not been exposed to venlafaxine (either brand) before that date.
† At any time up to 1 y after the first switch.

Table 4 – Health outcomes for switchers vs. nonswitchers: Existing users of originator venlafaxine.

Outcome measure	Post-pre difference: Nonswitchers* (n = 9036)	Post-pre difference: Switchers* (n = 1176)	Difference-in-differences (95% CI)†	Significance (P)
Change in visits to the ED per person (30 d)	0.00	0.01	0.01 (–0.01 to 0.03)	0.24
Change in visits to the ED per person (6 mo)	0.00	0.04	0.04 (–0.02 to 0.1)	0.15
Change in hospital admissions per person (30 d)	0.00	0.01	0.01 (–0.01 to 0.03)	0.31
Change in annual number of hospital admissions per person	0.00	0.02	0.02 (–0.05 to 0.1)	0.65
Change in use of specialist outpatient services per person (30 d)	–0.01	–0.03	–0.02 (–0.07 to 0.03)	0.47
Change in annual use of specialist outpatient services (visits per person)	–0.17	–0.77	–0.6 (–1.2 to –0.05)	0.03
Change in composite outcome (6 mo)‡	–0.06	–0.33	–0.28 (–0.6 to 0.01)	0.06
Change in number of unique prescriptions per person per year	0.00	0.04	–0.04 (–0.4 to 0.4)	0.99

CI, confidence interval; ED, emergency department.
* A switcher is a patient changing from originator to generic venlafaxine. Nonswitchers did not make a change in brand.
† Analysis using propensity score matching among the existing user group was also conducted (n = 1176 matched pairs), producing the same overall findings.
‡ Composite outcome = all contacts made with the health system combined (ED use, hospitalizations, and outpatient specialist services).

differences could be found [35]. A study from the United States found that rates of discontinuation were similar for brand and generic brand antidepressants including venlafaxine but that short-term health care costs and pharmacy costs were lower in new generic users [36].

Although consistent with the findings of the limited available research on venlafaxine, the present study extends the existing literature in several important ways. The number of patients included in this study—some 1600 switcher and 14,000 nonswitcher patients—greatly exceeds that in bioavailability studies, which often also only use healthy volunteers, adding certainty to the findings. Also, in the context of New Zealand, this study capitalizes on national policies that, when enacted, affect the total population. When a change is made in the New Zealand Pharmaceutical Schedule, such as that of venlafaxine, conditions of a natural experiment exist, whereby the total affected population (users of venlafaxine) is exposed to the same intervention (availability of generic venlafaxine) outside of the researcher's control: a controlled clinical trial would struggle to achieve similar parameters.

Despite these strengths, there are a number of important limitations that need to be considered when interpreting the findings of the present study. As an observational study using health care databases, randomization is not possible, making the evaluation of potential confounders all the more important [37,38]. The intergroup variability between switchers and nonswitchers found in this study was limited to a single variable each (out of seven measures) among existing originator and new generic users and two variables among new originator users. Correlation of these variables with the likelihood to switch was so low as to be negligible (see Table 2). Misclassification or incompleteness of data cannot be ruled out in these databases; however, the PHARMS database is an administrative database used for reimbursements to the pharmacy and, together with the special authority (SA) requirements, improves the reliability of the data. This study has been able to focus only on originator-to-generic brand switching and not on generic-to-originator brand switching because of the low uptake of generic venlafaxine in new users. Retrospective sample size calculations indicate that for a power of 80% a population size of around 400 would be

Table 5 – Health outcomes for switchers vs. nonswitchers: New users of originator venlafaxine.

Outcome measure	Post-pre difference: Nonswitchers* (n = 3371)	Post-pre difference: Switchers* (n = 448)	Difference-in-differences (95% CI)	Significance (P)
Change in visits to the ED per person (30 d)	0	–0.02	–0.01 (–0.05 to 0.02)	0.56
Change in visits to the ED per person (6 mo)	0.03	0.1	0.08 (–0.002 to 0.2)	0.17
Change in hospital admissions per person (6 mo)	0.01	0.02	0.01 (–0.06 to 0.09)	0.75
Change in use of specialist outpatient services per person (6 mo)	0.07	0.2	–0.13 (–0.48 to 0.22)	0.47
Change in composite outcome (6 mo)†	0.23	0.19	–0.04 (–0.4 to 0.4)	0.85

CI, confidence interval; ED, emergency department.
* A switcher is a patient changing from originator to generic venlafaxine. Nonswitchers did not make a change in brand.
† Composite outcome = all contacts made with the health system combined (ED use, hospitalizations, and outpatient specialist services).

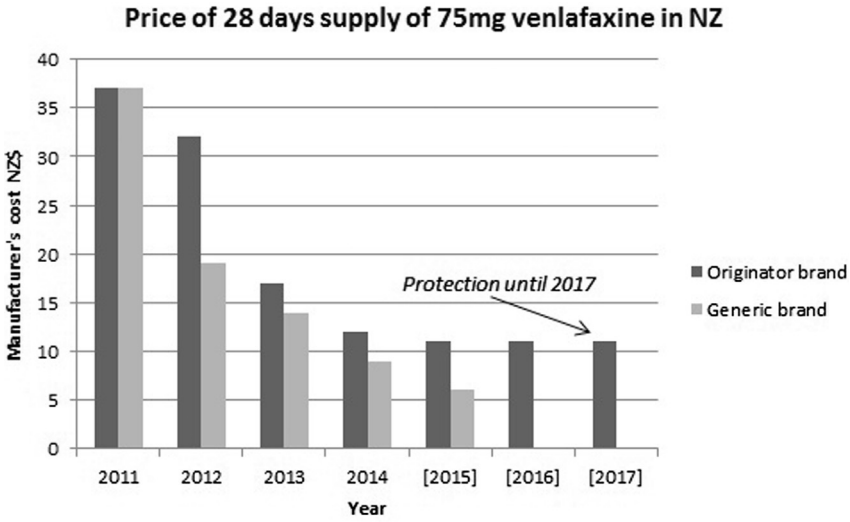

Fig. 2 – Price of 28 days' supply of 75 mg venlafaxine in New Zealand.

required to detect outcomes adequately among new generic venlafaxine users [39].

A follow-up period of 12 months was chosen in the case of existing users, being a period long enough to detect any health outcomes consequent to switching, and to accommodate any seasonality variation. In the case of new users, the difference-in-differences comparison could be made for only up to 6 months because the inclusion criteria required patients not taking venlafaxine at any time in the preceding 12 months and for at least 6 months (only) from the policy index date.

Due in part to changes in the method of funding at the primary care level, data on individual patient-general practitioner visits were not captured at a central level during the study years. This means that data are not available to indicate contacts made with either the dispensing pharmacy or the general practice in relation to brand switches. It is possible that a patient would seek reassurance from both the pharmacist and the primary care physician if he or she considered a change in venlafaxine brand was problematic. This study uses two variables—the switch-back rate and the number of unique prescriptions/year—as an indirect measure of this effect based on the knowledge that up to 70% of all visits to the doctor in New Zealand result in a prescription being written [40]. Despite the fact that a dispensed medicine does not necessarily mean that the medicine has been taken, either as intended or at all, pharmacy databases are accepted as a close approximation of medicine use [37].

Implications

Switching to generic venlafaxine in this study occurred without any detectable increase in health services use, and so apparently did not impose any additional health costs. Considerable savings could have been made had the price of generic venlafaxine been negotiated to 50% of the originator on introduction and incentives to switch created. Approximately NZ $2 million (75 mg monthly dosage) in the first year might have been saved with complete switching to generic venlafaxine at 2012 prices (see Fig. 2). It is thus worth exploring the barriers to switching, or lack of incentives to switch, within the context of this study.

At the introduction of generic venlafaxine, no incentive existed to promote its use. Despite this, 1 in 10 patients switched from originator to generic venlafaxine. Before September 2013, there was no incentive for either the doctor or the patient to choose which brand of venlafaxine to use because both brands were subject to the same SA approval process. Since late 2013, however, generic venlafaxine no longer requires an SA for prescribing and subsidy, and this should act as an incentive for doctors to prescribe generic venlafaxine. Existing patients can continue to receive the originator brand fully funded if their doctor renews the SA (given for 2-year periods), and because direct-to-consumer advertising is permitted in New Zealand, the supplier of the originator brand encourages patients to insist on this [41]. A similar situation existed in Sweden whereby the absence of demand-side activities to encourage the use of generic venlafaxine led to no change in utilization. An increase in the use of venlafaxine, however, was observed when prescribing of duloxetine was restricted, and near-complete generic prescribing of venlafaxine was achieved in 2011 once subsidy of the originator brand was removed in 2009 [42]. This removal of the subsidy in Sweden tested "brand worship" [43], whereas New Zealand has continued to fully subsidize the originator brand, leaving patients (in theory) with the choice of brand. Belgium too instituted preferential reimbursement for generic SSRIs, yet found that marketing strategies—including the introduction of pseudogenerics and prescribing and consumer brand loyalty—threatened the economic gains made by the policy [44].

Pharmacies in New Zealand are contracted by the District Health Boards to provide services to patients, including dispensing medicines for which pharmacies are reimbursed. At the time of this study, reimbursements for medicines dispensed were subject to a complex formula, but which in essence were calculated as a proportion (4%) of the price as gazetted in the PHARMAC Schedule [45]. Thus, a disincentive to switch patients to the less expensive generic venlafaxine now exists for pharmacy owners. This is reflected in the findings that 30% of the pharmacies in this study did not dispense generic venlafaxine at all, a stance PHARMAC has cautioned pharmacy owners against [5]. Whether it is the pharmacy or the patient making a choice to switch or not is unclear; however, it is clear that 60% of generic users switched (or were switched) to the originator brand. Pharmacists are within the bounds of New Zealand law if they switch brands provided they inform the patient of the change; the patient's consent, although implied, is not specifically required, and the prescribing doctor need not be informed either [46]. With the incentive remaining in favor of dispensing the originator brand, and the law facilitating both an originator-to-generic and generic-to-originator switch, it is likely that the use of generic venlafaxine will be limited until differences in the

price are decreased and specific measures are taken to encourage generic prescribing and to counter direct-to-consumer advertising. It may be that additional policy measures should be implemented to minimize incentives for multiple switching and reverse switching, and prescribers, as key opinion leaders, could take the lead in promoting generics to their patients.

In summary, this study provides evidence for the safety of originator-to-generic venlafaxine switching, yet raises issues regarding the roles of the patient, prescriber, and pharmacist in brand switching within the New Zealand context. Monitoring around the time of the switch may be prudent [47], but probably unwarranted if health practitioners and patients are adequately engaged in the switch process. Specific measures will need to be taken to increase the use of generic venlafaxine if potential savings are to be made to New Zealand's pharmaceutical expenditure.

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Supplemental Materials

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