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Study of mental health outcomes associated with different brands of venlafaxine at the Kumeu medical centre from January 2017 to October 2018

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Abstract

Background: The antidepressant venlafaxine has been available in New Zealand for two decades and is funded by the New Zealand Drug Purchasing Agency PHARMAC. This audit aimed to determine whether change to a different funded generic formulation of venlafaxine affected patient responses to venlafaxine.

Methods: A retrospective review of patient records for all patients at Kumeu Medical Centre, Auckland, New Zealand who received a prescription for venlafaxine since January 2017 was performed. Outcomes for patients who had experienced a stable positive clinical response to either of the two previously funded venlafaxine formulations and who were switched to the newly funded formulation were summarised.

Results: Of 49 patients who had been prescribed venlafaxine, 34 patients were excluded; 15 patients had experienced a stable positive clinical response to either of the two previously funded venlafaxine formulations and switched to the newly funded formulation. Of these, 12 (80%) had poor outcomes following the change in venlafaxine formulation. Nine patients switched back to the original brand venlafaxine and showed improvement in clinical symptoms.

Conclusion: These cases, reported from a single general practice, should be sufficient to call attention to the possibility of loss of effectiveness for patients treated with a funded generic brand of venlafaxine, and the need for further research.

Keywords: depression, generic, mental health outcomes, real-world, venlafaxine

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Introduction

The antidepressant venlafaxine has been available in New Zealand for two decades and is funded by the New Zealand Drug Purchasing Agency PHARMAC. Venlafaxine's pharmacological profile as a serotonin-noradrenaline reuptake inhibitor (SNRI) has made the medicine a useful treatment option for depression.[1] The Star D study, looking at a sequenced treatment of depression in primary care, utilised venlafaxine as a switching option after citalopram for patients who had failed a number of other treatments, and found a response rate of 28%, with 25% of patients reaching full remission.[2–4] Venlafaxine is therefore regarded as an important medicine in the treatment of depression, in particular for patients who do not respond to selective serotonin reuptake inhibitors (SSRIs), and forms part of the treatment recommendation of the Australian and New Zealand Royal College of Psychiatrists guideline for the treatment of depression.[5]

PHARMAC annual reports have highlighted venlafaxine as 1 of its top 20 pharmaceutical medicines by cost.[6] The development of generic formulations of venlafaxine lead PHARMAC to

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initially approve a generic brand 'Arrow-Venlafaxine XR' as a funded medicine alongside the original 'Efexor XR' brand. The funding decision was criticised by Lessing and colleagues,[7] as the switch was cost neutral with no incentive for prescribers or patients to move to a less expensive formulation. In 2017, PHARMAC changed funding to a sole supply thereby making another generic formulation, 'Enlafax XR', the only funded brand of venlafaxine.

The role of PHARMAC in the New Zealand medicines landscape has resulted in numerous generic substitutions for many years now. It has been a very valuable cost saving strategy for the country's pharmaceutical budget, and both doctors and patients have become accustomed to this as part of health care within New Zealand. However, in September–October 2017, a number of patients at the Kumeu Medical Centre, Auckland, New Zealand who had previously been mentally well on venlafaxine experienced recurrence of their symptoms over a period of 0.5–5 months after switching to the newly funded generic brand. The experience of several of these patients was so striking and unexpected for both patient and general practitioner that, in the absence of any plausible explanation for the change in their mental state, these patients were invited to consider paying the surcharge and reverting to their previous brand. The New Zealand media was alerted to similar patient experiences, and reported this on 28 February 2018,[8,9] and again in April 2018.[10]

To better characterise the clinical changes in patients who switched to the replacement funded venlafaxine formulation, and the potential association with this venlafaxine formulation, records of all patients at the Kumeu Medical Centre who had received a prescription for venlafaxine since January 2017 were reviewed.

Methods

All patients who had received a prescription for venlafaxine between 01 January 2017 and 03 October 2018 were identified in a retrospective review of records held at the Kumeu Medical Centre, a semi-rural practice on the outskirts of Auckland City. Patients included in the audit of outcomes were those with ongoing continuity and documentation of all aspects of health care at the Kumeu Medical centre, and who had an established clinical response to either of the two previously PHARMAC-funded venlafaxine brands and who had subsequently been changed to the newly funded brand. Patients were considered to have an established clinical response if symptoms related to mood disorder were no longer an active problem in the patient's clinical care. Patients excluded from the audit included those who had not already experienced an adequate clinical response to any brand of venlafaxine, patients who had only been briefly prescribed venlafaxine (less than 4 weeks), patients who never changed brands, patients with significant substance abuse disorders, patients receiving other major concurrent treatment interventions, which may have modified or confounded the treatment response, and patients who were lost to adequate follow up (at least 5 months) after the change in venlafaxine brand.

Informed verbal and signed consent was obtained from patients to perform the audit and publish the results. A careful review of clinical notes was conducted to assess the patients' subsequent clinical course following the change in funded venlafaxine brand. The audit identified whether the patient had previously been prescribed other antidepressants, what brand of venlafaxine the patient had been prescribed at the time of the change, as well as the dose and duration of treatment with the newly funded venlafaxine brand. Prescribing information, including the date on which venlafaxine (Enlafax XR) was dispensed, was corroborated by dispensing data obtained from the national database of pharmaceutical dispensing 'Testsafe'. The clinical status of patients before the switch to the replacement funded venlafaxine was extracted, as well as patient- and/or general practitioner-based perception of treatment outcomes after the change in venlafaxine brand. Outcomes of patients who had responded poorly to the replacement brand venlafaxine were summarised, and the time frame of this clinical response was also reviewed. Finally, these latter patients were telephoned and surveyed regarding the change to their brand of venlafaxine. Responses were solicited to the questions: 'Did you have any concerns about it being a different brand when it was prescribed?' and 'Were you aware of any publicity around Enlafax at the time the issue of its effectiveness came up in the consultation?'

Results

The review of patient records identified 49 patients who had been prescribed venlafaxine; 34 patients were excluded from the audit (Figure 1),

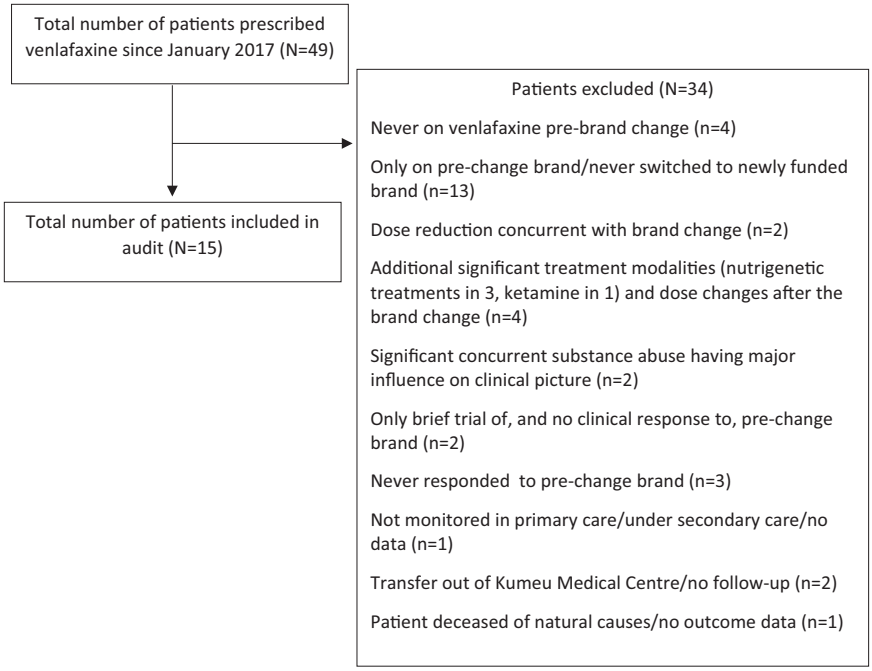

Figure 1. Patient disposition. Of the 15 patients identified, 1 had no prior treatment with antidepressants before initiation of venlafaxine, 3 patients had been previously exposed to one antidepressant, 6 patients had been trialled on two other antidepressants, and 5 patients had been treated with three to five prior antidepressants (Table 1). In the audit sample, 12 patients were stable and well on 'Efexor XR' and 3 on 'Arrow-Venlafaxine XR' before receiving 'Enlafax XR'. Patients were receiving a daily dose of venlafaxine ranging from 37.5 mg to 225 mg (average daily dose was 167.5 mg; Table 1).

leaving 15 patients who had experienced a stable positive clinical response to either of the two previously funded venlafaxine brands and who were switched to the newly funded brand and had relevant data. The 15 patients included in the audit (Table 1) comprised 6 women and 9 men aged from 23 to 72 years who had been treated with venlafaxine for between 1 month and 11 years with an average treatment duration of 5.5 years prior to the switch. For three patients, the length of exposure to venlafaxine was unknown prior to the change in brand.

In Table 2, post-formulation change data for patients who changed to the newly funded brand of venlafaxine is noted, with a contemporaneous comment either from the patient or the general practitioner, extracted from the medical record. These patients had a total of 20–73 weeks of follow-up data following the change in venlafaxine brand. Of the 15 patients, 3 managed the switch without any recorded problems. The audit identified 12 patients (80% of audited patients) who experienced some negative change in their mental status following initiation of the newly funded brand of venlafaxine. The changes in mental status varied from a 'few low days' (not previously experienced when on original brand venlafaxine) in one patient, to significant symptom clusters including depression, increased irritably, anger, tiredness and 'dark thoughts'. Loss of treatment effectiveness was the only effect noted by the patients. No other side effects were mentioned in relation to the change in brand, and no discontinuation effects were evident. The date on which venlafaxine was prescribed, and the time at which the change in efficacy was detected by the patient, was before media attention surrounding the issue in all 12 patients who developed signs of a poor response to the replacement funded venlafaxine (Table 3). No patient who responded to the question regarding awareness of any publicity around Enlafax was aware of any adverse publicity surrounding the dispensed brand of venlafaxine (Table 3). Follow-up findings of the 12 patients who developed signs of a poor response to the replacement funded venlafaxine are summarised in Table 4. Three of these patients remained on the replacement funded venlafaxine, one of whom was receiving an increased dose of venlafaxine (300 mg daily). One patient wished to switch back to the original brand venlafaxine but was unable to do so on account of the cost of the unsubsidised brand. Of the 12 patients, 9 chose

Table 1. Patients who had experienced a stable positive clinical response to either of the two previously funded venlafaxine brands and who were switched to the newly funded brand and were included in the audit.

Patient	Age (years)[a]	Brand and daily dose prior to change	Prior antidepressant treatment	Duration of treatment pre-switch (months)	Pre-switch treatment effective?
Male 1	54	Efexor XR 225 mg		72	Yes
Male 2	50	Arrow-Venlafaxine XR 187.5 mg	Amitriptyline, citalopram	14	Yes
Male 3	52	Efexor XR 225 mg	Fluoxetine	108	Yes
Female 1	36	Efexor XR 75 mg	Escitalopram, bupropion	50	Yes
Male 4	31	Efexor XR 225 mg	Fluoxetine, nortriptyline, citalopram	93	Partial response[b]
Male 5	72	Efexor XR 150 mg	Citalopram, escitalopram	80	Partial response
Female 2	61	Efexor XR 150 mg	Paroxetine, citalopram, fluoxetine	112	Yes
Male 6	26	Efexor 225 mg	Methylphenidate, citalopram	Unknown	Yes
Male 7	26	Arrow-Venlafaxine XR 75 mg	Methylphenidate, venlafaxine, nortriptyline, escitalopram, mirtazepine	4	Yes
Male 8	58	Efexor XR 150 mg	Citalopram, nortriptyline	85	Yes
Female 3	23	Arrow-Venlafaxine XR 37.5 mg	Fluoxetine, mirtazapine	unknown	Yes
Female 4	51	Efexor XR 150 mg	Paroxetine	76	Yes
Male 9	53	Efexor XR 225 mg	Paroxetine, nortriptyline, citalopram	unknown	Yes
Female 5	33	Efexor XR 112.5 mg	Bupropion	1	Yes
Female 6	50	Efexor XR 300 mg	Fluoxetine, nortriptyline, citalopram, venlafaxine	134	Yes

[a]Age at the time of review of medical records (3 October 2018).
[b]The patient was responding to venlafaxine but experienced a reactive depression following the death of a close relative. Recovery from this episode was occurring during the lead-in period prior to switching to the newly funded brand.

to switch back to the original brand of venlafaxine, and all patients reported remission of the emergent symptoms they had experienced when switching to the replacement funded venlafaxine.

Discussion

Venlafaxine is a somewhat unique antidepressant. Termed a SNRI, it has a broad engagement with the monoamine neurotransmitter system. Acting as a serotonin reuptake inhibitor and a noradrenaline reuptake inhibitor, among other actions, it upregulates serotonergic and noradrenergic function. As the noradrenaline transporter protein also has a strong affinity for dopamine, its inhibition also leads to increased dopamine availability, especially in the prefrontal cortex.[11] Venlafaxine is important because there are patients with particular clinical profiles that respond very well to this drug, who do not respond well to any other

Table 2. Clinical response of patients since commencement the newly funded brand of venlafaxine, initiated at the pre-switch daily dose.

Patient	Age (years)[a]	Was replacement venlafaxine effective?	Duration of replacement venlafaxine treatment (weeks)	Comment since the change
Male 1	54	No	50	Episodes of low moods every 3 weeks, increased irritability; no change with dose increase
Male 2	50	No	18	A few low days
Male 3	52	Yes	68	Didn't notice any change
Female 1	36	No	21	Feels down, low days, more easily stressed
Male 4	31	No	13	Very low, feels angry and volatile, increased anxiety and fear
Male 5	72	Yes	24	No change evident[b]
Female 2	61	No	54	Feels very tired, increasing depression since switching
Male 6	26	No	70	Not as effective
Male 7	26	No	18	Doesn't feel new formulation is working
Male 8	58	No	21	Not so good, needing to sleep more again
Female 3	23	Yes	49	Probably not a significant change[c]
Female 4	51	No	66	More depressed
Male 9	53	No	12	More irritable, more anxious, not sleeping so well
Female 5	33	No	5	Drop in mood, still unhappy with increased dose, feels she is back where she was at the start; drinking more
Female 6	50	No	72	Mood dropped since generic, anxiety got worse

[a]Age at the time of review of medical records (3 October 2018).
[b]Despite no change in efficacy following the switch to the newly funded brand of venlafaxine, the patient chose to change back to the original brand of venlafaxine for the remainder of the 60-week follow up without further change in clinical response.
[c]The patient changed back to the original brand of venlafaxine at 49 weeks because of a dip in mood that could not be directly attributed to the earlier switch in venlafaxine brand. The patient stabilised for the remainder of the 65-week follow up.

available antidepressant. Many of the patients who respond to venlafaxine have had a succession of failed treatments and are a generally more treatment-resistant subgroup. This is evidenced by the large number of different psychotropic drugs used previously by the patients in this study – a total of 31 different medications tried amongst 15 patients. It is further evidenced by results of a meta-analysis of randomised controlled trials comparing the efficacy and acceptability of 21 antidepressant drugs for the acute treatment of major depression. Venlafaxine came in as the

Table 3. Temporal information regarding the prescription of venlafaxine in patients who had a poor response to the replacement funded venlafaxine and patient perceptions of the replacement brand.

Patient	Date 'Enlafax XR' prescribed	Date loss of efficacy reported in patient notes	Approximate time to detection of change in efficacy by patient[a]	Patient awareness of adverse publicity to change in venlafaxine brand	Patient concerns regarding change in venlafaxine brand
Male 1	25 May 2017	17 October 2017	5 months	No	No
Male 2	7 June 2017	4 October 2017	4 months	No	No
Female 1	12 September 2017	11 December 2017	3 months	No	No
Male 4	8 May 2017	12 August 2017	2 months	No	No
Female 2	19 September 2017	13 March 2018	⩽1 month	No	Yes
Male 6	30 May 2017	13 November 2017	⩽1 month	No	No
Male 7	16 June 2017	24 October 2017	2 months	No	No
Male 8	14 June 2017	13 November 2017	2–3 months	No	No
Female 4	20 June 2017	25 September 2018	⩽3 months	No	No
Male 9	13 July 2017	4 October 2017	⩽3 months	No	No
Female 5	16 June 2017	26 June 2017	⩽2 weeks	No reply	No reply
Female 6	12 May 2017	20 October 2017	⩽1–2 Months	No	No

[a]Time from first dose of replacement brand venlafaxine.

fourth most efficacious antidepressant, surpassing all of the SSRIs.[12]

This review of our records revealed that 49 patients were prescribed venlafaxine during or after January 2017. Of these 49 patients, 34 did not meet our study criteria and were excluded from analysis for reasons related to incomplete follow up or the presence of extraneous variables that may have influenced the outcome of the change in formulation. Of the 15 remaining patients, only 3 reported no change in their well-being when switched to the replacement funded formulation; 12 patients had documented evidence of a decline in their mental health dating from several weeks after changing to the newly funded generic brand. No patients complained of any side effects with the switch in brands, other than loss of effectiveness. Changes in the mental health of patients may have been related to altered serum levels causing some withdrawal symptoms that could have adversely affected the patient's mental state. However, none of the patients studied reported discontinuation symptoms at the time of the switch in formulation, with decline in mental functioning typically reported from between several weeks to several months after the change.

This study is naturally limited by the small numbers in a single General Practice and the lack of consistent use of a standardised clinical assessment tool. The patients were all very well known to the practitioner, there was absolute continuity of care, and the patient's progress was being closely observed (four of the patients that were originally prescribed venlafaxine were excluded from the audit on the grounds of incomplete follow up). Nevertheless, despite this close observation, a number of patients were aware of a loss of effectiveness with their venlafaxine between 3 and 12 months before reporting it to the practitioner (as reflected in the patient notes). We believe that, in these instances, it took both the patient and practitioner time to realise that there may have been a change in drug effectiveness, particularly as the loss of effectiveness generally seemed to be an incremental process.

Table 4. Results for patients who had a poor response to the replacement funded venlafaxine.

Patient	Brand at the end of audit	Daily dose	Duration of follow up on final venlafaxine brand (weeks)	Duration of follow up post-switch to replacement funded venlafaxine (weeks)	Comments
Male 1	Enlafax XR	225 mg	50	54[a]	Restricted by cost. Would prefer to switch to Efexor XR as had experienced immediate improvement when initiated on that formulation
Male 2	Efexor XR	150 mg	46	64	All good; no problems
Female 1	Efexor XR	75 mg	42	63	Mentally very good
Male 4	Efexor XR	225 mg	60	73	Doing quite well
Female 2	Efexor XR	150 mg	29	54	Mental health good
Male 6	Enlafax XR	225 mg	70	70	Not as effective; restricted by cost
Male 7	Efexor XR	75 mg	51	69	Felt better overnight
Male 8	Efexor XR	150 mg	47	68	Feel less tired, happy with switch back and wants to stick to it
Female 4	Efexor XR	150 mg	4	70	Noticed positive change since switching back: 'know I am not losing my mind'
Male 9	Efexor XR	150 mg	51	63	Helped him, happy with how his management had gone; no overt side effects
Female 5	Efexor XR	150 mg	15	20	Better
Female 6	Enlafax XR	300 mg	72	72	Dose increased to 300 mg to manage symptoms

[a]It appears that the patient did not collect the final venlafaxine prescription, as per the audit.

The clinical observations demonstrated by this study present us with somewhat of an enigma. An on-line questionnaire directed at patients who visited the PHARMAC venlafaxine website in 2017 did not reveal any significant perceived difference in effectiveness for patients switching to the replacement funded formulation.[13,14] However, a self-selected group responding to a questionnaire on the PHARMAC website is a very different study methodology from this audit of a closely followed group of patients who had previously had an enduring clinical response to a different formulation of venlafaxine. The study by MacKrill and Petrie linked perception of increased side effects to perceived loss of effectiveness of the switched formulation[13]; however, no patients in this audit experienced any side effects. MacKrill and Petrie also linked loss of effectiveness to negative perceptions of generics or lack of trust in pharmaceutical agencies; however, again this was not evident in 14 out of the 15 patients studied. Patients with depression are susceptible to nocebo effects; however, a study that examined treatment emergent adverse effects in the placebo arms of multiple clinical trials of an antidepressant found no evidence linking nocebo effects with adverse clinical outcomes.[15]

The New Zealand Medicines and Medical Devices Safety Authority Medsafe, which is

responsible for the regulation of medicines in New Zealand, had been satisfied that there was nothing unusual about the increased number of reports that followed in the wake of the switch to sole supply for the replacement funded brand.[16] The notifications were also independently reviewed by the Medicines Adverse Reactions Committee (MARC). A study has subsequently been published suggesting that the spike in reporting of side effects and complaints of reduced therapeutic effect following the change in venlafaxine brand that followed media attention to this issue on 28 February 2018, and again in April 2018, was an example of the nocebo effect.[17] However, no patient in the current audit was aware of any media attention to this issue when the matter was raised with them in recent months, and in 10 of the 12 patients who experienced the apparent loss of effectiveness, the relevant clinical observations were recorded in the patient notes between August and December 2017, prior to any public attention to the issue (Table 3). Only 1 of the 15 patients in the audit admitted to any concerns about the change in venlafaxine brand (Table 3). A substantial number of patients in New Zealand had already transitioned to the previously funded generic brand ('Arrow-Venlafaxine XR'), including 3 of the 15 patients in this audit, without any concerns by either patient or clinicians. As all patients in New Zealand have long been accustomed to chopping and changing their medication brands across almost every therapeutic class of drugs, this seems to rule out a nocebo effect for all but a tiny minority, who New Zealand general practitioners are well used to spending time re-educating. The subsequent positive clinical response upon reverting back to the original venlafaxine brand could be attributed to a placebo effect fuelled by the general practitioner's suggestion. However, the time frames of clinical response were generally in line with the expected pharmacological response to antidepressant medication. In the author's experience, patients with severe lifelong mood disorders who have previously tried numerous different treatment regimens do not respond very well to placebos, or, if they do, the duration of effect is short-lived. This is backed by the most recent review of the placebo effect by the Cochrane Collaboration,[18] which found no significant effect on treatment outcomes with placebo for depression, when trials randomise active treatment against both placebo treatment and no treatment control groups. Furthermore, having to pay a significant part charge is in itself a considerable ongoing test of the veracity and magnitude of the clinical response experienced by the patient. For a number of these patients, resuming treatment with the original venlafaxine brand was a significant financial stress.

The most obvious mechanism for loss of clinical effectiveness, if we are to assume the products are molecularly identical, is reduced bioequivalence. Generic medications are not subjected to the same rigorous efficacy and safety testing as the original branded drugs. They are generally tested in healthy volunteers, and without requirement to produce clinical efficacy data. Therapeutic and pharmaceutical equivalence is assumed by meeting set standards of bioavailability including maximum drug plasma concentrations and area under the drug concentration-time curve for which the industry standard is 80–125% of the originator brand levels. The first patient (Female 5) that we encountered with serious recurrence of her symptoms several weeks after switching to the replacement funded venlafaxine brand did not respond to a daily dose increase of 37.5 mg above the prior established effective dose of 112.5 mg – that is, a total of 150 mg/day and a relative dose increase of one-third. She proceeded to a complete recovery when put back on the original venlafaxine brand. A second patient (Male 1), also did not respond to increasing the daily venlafaxine dose from 225 mg to 300 mg (something the patient self-initiated) after switching formulation. Because of this initial experience, and the serious nature of the condition in question, no further attempts were made to manipulate venlafaxine doses with the replacement funded formulation, and all patients who had experienced a decline in their wellbeing were offered the option of going back onto the original venlafaxine brand.

With regard to bioequivalence, the Medsafe website details evidence from four studies that do indeed show bioequivalence of 'Efexor XR' and 'Enlafax XR' serum levels for both venlafaxine and its active metabolite O-desmethylvenlafaxine.[14] However, these studies are either unpublished or unable to be retrieved on PubMed. There are a number of published studies looking at therapeutic equivalence of various brands of venlafaxine (not the generic in question for this audit) with no particular issues identified, as well as one study that identified unacceptable variation in bioavailability and increased side effects.[19] Initial trials in the 1990s showed significant differences in efficacy between immediate-release and extended- or controlled-release venlafaxine formulations and,

despite equivalent dosing, the extended-release product was superior after 8 and 12 weeks of therapy.[20] The reasons for this variance are most likely differing levels of both venlafaxine and the primary active metabolite O-desmethylvenlafaxine and metabolism of these entities to the inactive metabolite N-desmethylvenlafaxine and subsequent excretion.[21] A naturalistic therapeutic drug monitoring study was conducted using two different formulations of venlafaxine in two different in-patient wards in a university hospital in Germany. Whilst the mean values of venlafaxine and O-desmethylvenlafaxine overall did not differ between formulations, differences were observed in serum concentrations of active drug with regard to patient age and gender with one formulation and with regard to smoking status with the other formulation, which the authors suggested 'could endanger safety and efficacy of drug use'.[22]

A further issue that may create considerable individual variability in response to venlafaxine is the number of common genetic polymorphisms of the cytochrome P450 enzyme CYP2D6. Venlafaxine is metabolised into its more active metabolite O-desmethylvenlafaxine by CYP2D6, and variations in gene expression mean there are poor, intermediate and rapid metabolisers. Expression of CYP2D6 polymorphisms with regard to venlafaxine metabolism was studied in an Indian population using metabolic ratios of venlafaxine to O-desmethylvenlafaxine in 141 healthy subjects.[23] Approximately 13% were poor metabolisers, 83% were extensive metabolisers and 4% were defined as ultra-metabolisers. This does suggest that the clinical effect of minor variations in the bioavailability of venlafaxine, perhaps more than other drugs, could be amplified by common individual genetic variations especially in CYP2D6.

A recent literature review that focussed on switching medication products during the treatment of psychiatric illness highlighted that 'bioequivalence demonstrated after single dose studies may not be operant under steady state conditions. Failure to assess the impact of product specific (e.g. excipients) and patient specific (e.g. comorbidities, concurrent medications, smoking status) factors during the approval process for generic products may set up a situation where bioequivalence may not translate into therapeutic equivalence.' [24]

An earlier review of the literature concerning adverse effects of brand switching identified psychotropic drugs as being particularly vulnerable to these issues.[25] A study looked at suicide rates for brand *versus* generic formulations across four different psychoactive drugs, and found for the antidepressant sertraline a significantly lower hazard ratio for the originator brand. Suicide rates for the other three drugs were also lower in the originator brand, but did not reach statistical significance.[26]

Subsequent to the switch to the generic version of venlafaxine in New Zealand, a similar sole supply status was conferred on a generic brand of the anticonvulsant and mood stabiliser lamotrigine. Issues of therapeutic equivalence became apparent, sufficient for PHARMAC to make the original brand readily available upon application by a clinician.[27] There is a growing literature highlighting these concerns for medications that influence the central nervous system, and this may be especially pertinent with respect to effects on mood. A study by Rahman *et al*. examined adverse drug reactions to lamotrigine and analysed them according to originator brand, authorised generic (which is pharmaceutically identical) and generic.[28] Whilst the reporting odds ratio (ROR) was the same across these groups for most adverse reactions, for suicidal ideation and completed suicide the ROR was increased fourfold in the generic group *versus* both the brand and the authorised generic group. The authors concluded from this that public perception bias against generics (nocebo effect) was not a factor, as the authorised generic drugs would also have been perceived by consumers as being 'generic'. It raises the question of the utility of the accepted criteria for bioequivalence (80–125%) and whether for drugs that either have a narrow therapeutic index, or that effect the central nervous system, the criteria should be more stringent. Generic drugs do not go through the same clinical trials as originator brands prior to approval, and are not required to demonstrate the same safety and efficacy data, but only pharmaceutical equivalence and bioequivalence. This means that post-marketing safety surveillance has an important role in ensuring the safety and efficacy of generic drugs and this may be especially true of antidepressant and anticonvulsant medications.

The authors of a New Zealand review of prescribing behaviour and outcomes when the first generic formulation of venlafaxine was initially made available (the Arrow-Venlafaxine brand) concluded that their study provided evidence for the safety of originator to generic venlafaxine switching, and

that the change occurred 'without any detectable increase in health services use, and so apparently did not impose any additional health costs'.[7] However, their measure of health outcomes was simply any change in hospital admissions, use of specialist outpatient services and deaths. The current audit has shown that outcome measures in monitoring such a change would need to be more comprehensive than just these indicators. The patients from the Kumeu Medical Centre who experienced loss of effectiveness endured a significant psychosocial and financial cost, as well as utilising more primary care resources than previously, although none required hospital admission or referral to secondary services.

It would probably not be feasible to resolve the question posed by this audit with a randomised trial of the generic venlafaxine 'Efexor XR' *versus* the originator 'Enlafax XR'. However, a small trial could be conducted in a sample of affected patients to determine the bioavailability of the two products after steady state is achieved. In the case of venlafaxine, this is reported to be 3 days, and during that time there is no risk of loss of clinical effectiveness for patients enrolled in the study. Both venlafaxine and O-desmethylvenlafaxine levels would need to be measured and, as already indicated, genetic variations in CYP2D6 could effectively amplify the significance of small variations in bioavailability so genotyping in this regard would also be informative.

Conclusion

Despite the acknowledged limitations of this small audit, these cases reported from a single general practice centre call attention to the possibility of loss of effectiveness for patients in New Zealand treated with the replacement funded brand of venlafaxine. In view of the destructive and potentially life-threatening nature of inadequately treated depression, and the importance and rather unique nature of venlafaxine in our therapeutic armamentarium, we believe urgent attention should be given to further investigation of this issue. Consideration should be given to alerting primary care, further investigating the therapeutic equivalence of the funded generic venlafaxine brand in a sample of apparently affected patients, and funding an alternative brand for patients who can be shown to have suffered a relapse of their condition after changing their brand of venlafaxine.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethical statement

Ethical approval was not required or sought for this clinical chart audit, as per the guidance for conduct of observational studies in New Zealand that can be found in 'Ethical Guidelines for Observational Studies. Observational research, audits and related activities: Revised edition, July 2012.' Available at: https://neac.health.govt.nz/system/files/documents/publications/ethical-guidelines-for-observational-studies-2012.pdf.

Informed consent

We have written consent from the 15 patients involved in this audit.

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