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ORIGINAL REPORT

Measurement of changes in antihypertensive drug utilisation following primary care educational interventions†

Fiona E. Horn BSc, MPH[1]*, John A. Mandryk BSc (Hons), PhD[1], Judith M. Mackson BPharm, MMedSci(Clin Epi)[1], Sonia E. Wutzke BSc (Psych) Hons, MPH, PhD[1], Lynn M. Weekes BPharm, MSc, PhD[1] and Rob J. Hyndman BSc (Hons), PhD, AStat[2]

[1]*National Prescribing Service Ltd, Surry Hills, Sydney, Australia*
[2]*Department of Econometrics and Business Statistics, Monash University, Melbourne, Australia*

SUMMARY

Purpose To measure changes in drug utilisation following a national general practice education program aimed at improving prescribing for hypertension.

Methods A series of nationally implemented, multifaceted educational interventions using social marketing principles focusing on prescribing for hypertension, was commenced in October 1999, and repeated in September 2001and August 2003. The target group was all primary care prescribers in Australia and interventions were both active (voluntary) and passive. Newsletter and prescribing feedback was mailed in October 1999, September 2001 (newsletter only) and August 2003. Approximately a third of general practitioners (GPs) in Australia undertook at least one active educational activity (clinical audit, educational visit or case study) during the period October 1999–April 2004. National dispensing data from 1996 to 2004 were analysed using time series methodology with a decay term for intervention effect, to assess trends in prescribing of various classes of antihypertensives. In particular, the program aimed to increase the prescribing of thiazide diuretics and beta blockers.

Results Consistent with key intervention messages, the program achieved an increase in low-dose thiazide and beta blocker prescribing. The rate of prescribing of low-dose thiazides doubled from 1.1 per 1000 consultations in October 1999 to 2.4 per 1000 in October 2003. Beta-blocker utilisation showed a more modest but significant increase over the time of the study, with the change in observed versus expected rate of prescribing increasing by 8% by April 2004. Therapeutic options for treating hypertension changed markedly in the time of the study with the advent of ACE inhibitor/Angiotensin II receptor antagonists and thiazide combination products. It is important, therefore, to interpret the results in light of these changes.

Conclusion A national education program aimed at GPs was successful in improving prescribing for hypertension. Lessons learned will be applied in evaluation of future NPS programs and are also applicable to analysis of other interventions aimed at influencing prescribing behaviour. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS — antihypertensives; primary care; educational interventions; time series analysis; decay; regression methods

INTRODUCTION

The National Prescribing Service Ltd (NPS) was established in 1998 to provide independent, evidence-based medicines information and education to health professionals and consumers. NPS targets therapeutic areas where prescribing problems, uncertainty or controversy have been identified as likely to result in sub-optimal health outcomes and/or increased costs and where education and information may have a positive impact.[1] Selection of interventions is based on a knowledge of barriers and facilitators to change in practice, and it is acknowledged that repeated interventions over time may be necessary in order to produce sustainable changes in behaviour.[2]

* Correspondence to: F. E. Horn, BSc, MPH National Prescribing Service Ltd, P.O. Box 1147, Strawberry Hills, Sydney, NSW 2012, Australia. E-mail: fhorn@nps.org.au
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Evidence and guidelines available in 1999 (when the first NPS program on the management of hypertension commenced) suggested that hypertension was under-diagnosed, under managed and that risk stratification (the process of combining a patient's individual risk factors to estimate their level of cardiovascular risk) was one way of improving hypertension management.[3–5] In addition, it was recognised that half of all hypertensive patients will need more than one drug to gain control. More recent survey data suggest that just under half of Australian general practitioners (GPs) find hypertension difficult to manage.[6]

Six main drug classes are used worldwide in the treatment of hypertension: thiazide and thiazide-like diuretics, beta-blockers, angiotensin converting enzyme inhibitors (ACE inhibitors), calcium channel blockers (CCBs), angiotensin II receptor antagonists (A2RAs), and alpha blockers. At the time of the interventions, there was no evidence of substantive differences between the drug classes with respect to effect on lowering BP. In addition, adverse effect profiles and data about effects on cardiovascular morbidity and mortality differed, and reliable evidence from randomised controlled trials also varied.

For each major class of antihypertensive drug, there are both compelling indications for use in specific patient groups as well as compelling contraindications. Available evidence at the time of the programs suggested that beneficial cardiovascular outcomes are achievable with low-dose thiazides and thiazide-like diuretics[7,8], thus this was one of the key messages of the NPS hypertension program.

The objective of this paper is to describe how changes in antihypertensive drug utilisation were measured following the national education program.

METHODS

Interventions

A series of nationally implemented multifaceted educational interventions using social marketing principles, focusing on hypertension prescribing, commenced in October 1999, and were repeated in September 2001 and August 2003 (Table 1). These interventions aimed to reach all prescribers in primary care, and included newsletters, prescribing feedback, educational visiting, clinical audit with feedback and case studies (paper-based and peer group discussion). The interventions were implemented over an extended period of approximately 6 to 8 months.

Key messages of the programs were: choose the class of antihypertensive based on the patient's risk profile; identify compelling indications and contra-indications; newer drugs are not always better than existing drugs; and patients have an important role to play in concordance with therapy and lifestyle. As a result of the interventions for managing hypertension, we expected specific changes in GP prescribing. These were:

- an increase in the use of thiazide or thiazide-like diuretics as first line therapy for hypertension (there was a sub-message in the first program to avoid indapamide which in October 1999 was not available in a low-dose formulation and therefore we did not expect an increase in use)
- an increase in the use of low-dose formulations where thiazide diuretics were used
- an increase in the use of beta-blockers as first-line therapy.

Data

Monthly dispensing data from an average of 19 600 GPs who rendered at least 13 consultations per month

Table 1. GP participation in NPS hypertension program

Participation: A = active*; P = passive		Number of GPs		
		†Oct. 1999	Sept. 2001	Aug. 2003
P	Newsletter	~17 000	~17 000	~17 000
P	Prescribing feedback	~16 000	—	~18 000
A	Clinical audit	1902	933	1063
A	Case study (paper or peer group discussion)	218	202	1375
A	Educational visiting	2237	184	1153

*Number of GPs who did at least one activity 1999–2003 = 6076 from a total population of 20 580[24].
†Start dates of active programs and mail-out dates for passive interventions.

for 93 months (July 1996 to April 2004) were obtained from a national administrative claims database Pharmaceutical Benefits Scheme (PBS) maintained by Medicare Australia (formerly the Health Insurance Commission or HIC). Only drugs which incur a government benefit are included in the PBS database, and hence less expensive drugs are not well represented (being below the general patient co-payment threshold for most of the population), with coverage for health card holders (primarily the elderly/low income) being the most complete because of their much lower co-payment threshold. Moreover, drugs are provided for free, or at lower cost, to the patient if they are dispensed after the patient has incurred a set expenditure in the calendar year, called the 'safety net' threshold.[9] While these claims data represent approximately 80% of all primary care prescriptions (personal communication, HIC), it is thought that prescribing patterns of the medications of interest in this study are well captured by the available data. Original prescriptions (and not repeats), by date of prescribing, were the subject of analysis, since any impact by NPS should be reflected in the prescribing decision of the doctor. Because the NPS programs targeted individual GPs, the prescribing data were summarised for analysis at the level of the GP as mean prescribing rates per 1000 consultations across GPs within each month. Numbers of consultations by GPs (used in rate calculations) were obtained from the Medicare Benefits Schedule (MBS) database. The number of consultations per month per GP was then linked to the PBS data by anonymous scrambled provider ID. Also calculated was the monthly mean proportion of low-dose thiazides as a proportion of all thiazides for each GP where there was at least one thiazide prescription in the denominator variable in that month.

The targeted antihypertensive drug classes (see appendix) were thiazide and thiazide-like diuretics and beta blockers. We also examined overall trends in antihypertensive prescribing in other classes; that is, ACE inhibitors, CCBs and A2RAs, and these classes in total with the thiazide diuretics and beta blockers as 'total antihypertensives'.

Statistical analysis

Since the prescribing data was highly seasonal,[10] it was necessary to allow for this in the analysis. Time series analysis of prescribing data was undertaken using a robust seasonal decomposition technique and regression modelling.[11,12] The seasonal decomposition procedure decomposed each data series into three components of trend, seasonal and remainder, and seasonally adjusted data were formed by subtracting the seasonal component.

The intervention model, which was then fitted to the seasonally adjusted data, included trend changes (with decay) at time of NPS interventions (newsletter and prescribing feedback) and incorporated a term, (with decay) for the number of GPs who had participated actively in the hypertension program. The model also included a correlated error term, which allowed for other changes in trend. Thus, the fitted model had the following form:

$$Y_t = \alpha_0 + \alpha_1 t + \sum_{i=1}^{3} \beta_i z_{t,i} + \gamma \mathrm{GP}_t + N_t$$

where Y_t represents the seasonally adjusted data in month t; the first part of the model $(\alpha_0 + \alpha_0 t)$ represents an underlying linear trend; the variable $z_{t,i}$ models the ith 'passive' intervention; the variable GP_t is a measure of participation in NPS-specific educational programs; and N_t is a first order autocorrelated error term.

The 'passive' intervention variables $z_{t,i}$ allow the trend to change at the time of intervention, but assume that the trend will eventually return to the original trend line. Thus, any intervention is assumed to have a temporary effect. This is achieved by defining the intervention variables as follows:

$$z_{t,i} = \|t - \tau_i\| exp\{-\lambda \|t - \tau_i\|\}.$$

where $\|t - \tau_i\| = max(0, (t - \tau_i))$, τ_i is the time of the ith intervention, and λ is a decay parameter estimated from the data.

The effect of active interventions is also made temporary and decaying. Let P_t denote the number of GPs who have undertaken an education program in month t. Then we allow the effect of the program to dissipate over time, by defining

$$\mathrm{GP}_t = \left(P_t + e^{-\lambda} P_{t-1} + e^{-2\lambda} P_{t-2} + \cdots + e^{-(t-1)\lambda} P_1\right)/1000.$$

Again, the value of λ determines the rate of decay for this variable. This approach assumes the same decay rates for active and for passive interventions.

Because of the collinearity between the various NPS interventions, it is difficult to separate out the individual effect of each intervention. However, we can measure the overall impact of the interventions by treating the four parameters (β_1, β_2, β_3, γ) as a group and testing them jointly using an F-test.

The model assumed that any intervention has only a temporary effect. The inclusion of a decay term was included to more realistically reflect the non-permanence of the intervention and was estimated from the specific data-series being analysed. The impact of intervention can be calculated for each month post intervention by subtracting the intervention model terms from the actual data giving 'adjusted values'. Thus the observed changes are relative to what was expected without intervention.

The model was estimated using non-linear least squares.[11] Significance was accepted where *p*-values were less than 0.01.

RESULTS

Participation

GP participation is detailed in Table 1. The most frequent activity was clinical audit (42%), followed by academic detailing/educational visit (38%) with smaller numbers (19%) participating in case studies (paper based or peer group discussion). A GP may have participated in more than one activity.

Trends in prescribing

During the analysis period, prescribing of ACE inhibitors and CCBs fell by approximately 4 prescriptions per 1000 consultations per month (Figure 1). Prescribing of thiazide diuretics decreased similarly although the true rate is overwhelmed by the advent of the first fixed-dose combination products in April 2000. Low-dose thiazide prescribing increased slightly as did beta blocker prescribing. A2RAs showed a steady rise after listing on the PBS in October 1997.

There was a significant increase in the mean prescribing rate of total antihypertensives during the period of the active and passive interventions ($p < 0.000$). Compared to the expected underlying trend in the prescribing of all antihypertensives (Figure 2 and Table 2), the model suggested a 5% increase in prescribing by October 2000 (from October 1999), an 11% increase by October 2002 and 13% by October 2003.

Contrary to the key messages of the program, there was a decrease in the mean prescribing rate of thiazide diuretics after the first intervention, and a continued decrease over the time period of the study, of approximately 30% (Figure 3).

Despite the observed decrease in overall thiazide diuretic prescribing, there was a significant ($p = 0.000$) increase in the prescribing of low-dose thiazides (Figure 4) that coincided with the three passive interventions. By March 2002, there was a change of 100% in the observed versus the expected prescribing of low-dose thiazides and a continued increase up until April 2004 when the increase in observed versus expected reached 190%.

There was a significant increase in the proportion of low-dose thiazides when a GP prescribed a thiazide

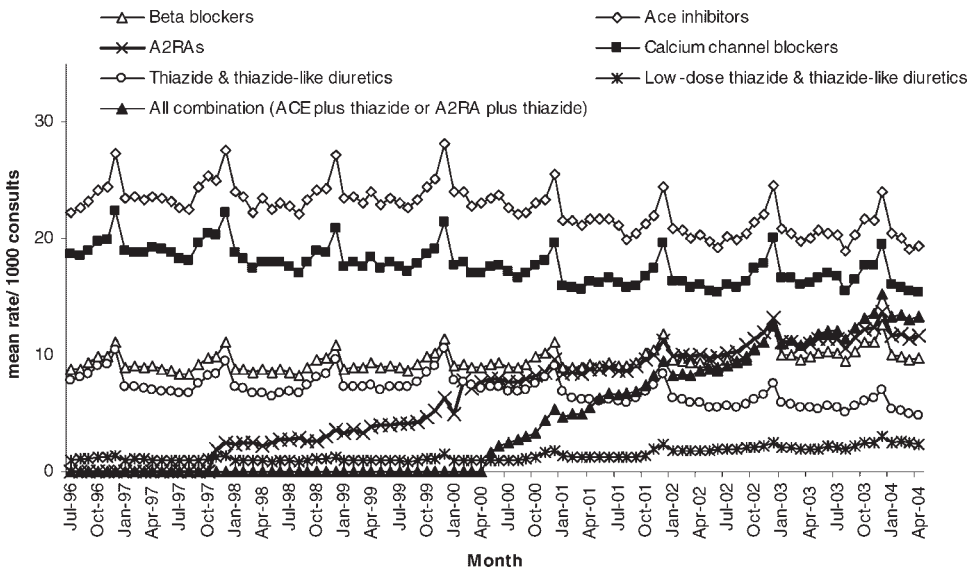

Figure 1. Mean prescribing rate of antihypertensive drug classes: July 1996–April 2004

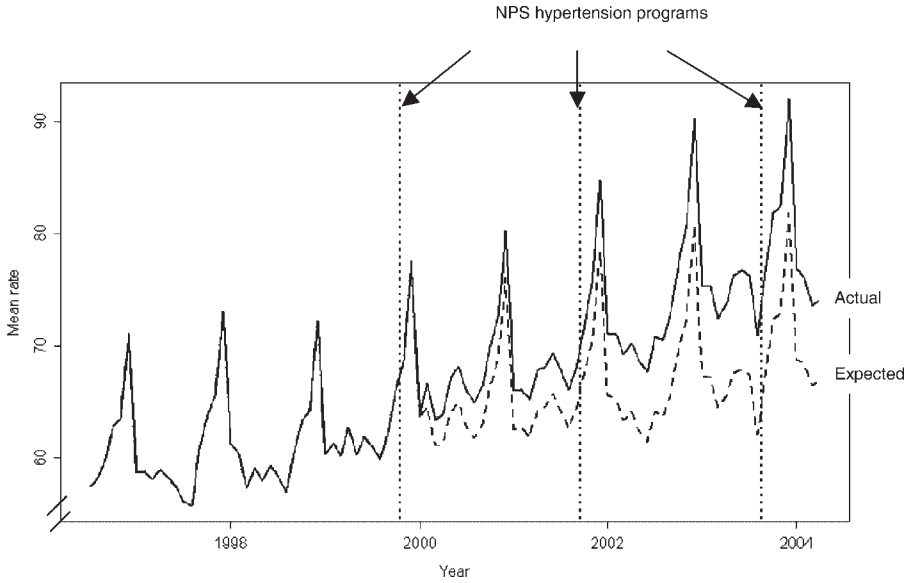

Figure 2. Mean prescribing rate of all antihypertensives—actual versus expected

diuretic (Figure 5). However, the calculation of this measure (and the changes in rates of thiazides and low-dose thiazides) was confounded by the advent of the combination products, which changed the denominator of available thiazides (Figure 6). Both analyses (Figures 5 and 6) show significant changes in observed versus expected changes with a 750% change up until April 2004 where combination products were included in the denominator, and 270% where the denominator included all thiazides only.

Beta blocker utilisation showed a more modest but still significant change over the time of the study, with the change in observed versus expected, reaching 8% by April 2004 (Figure 7.)

DISCUSSION

Consistent with key intervention messages, the program was associated with an increase in low-dose thiazide and beta blocker prescribing.

Interventions to influence prescribing occur within an environment where there are multiple influences, which are often not easily measurable. These include listing of new products/formulations, the influence of regulatory bodies, media, and consumer groups, release of clinical trial data and promotion from the pharmaceutical industry. Limitations of our drug utilisation data sources must also be considered when evaluating the impact of the NPS programs on hypertension prescribing.

While the PBS data files contain the most comprehensive national data set on prescriptions available, the dataset does have limitations. The general limitations of the data, including the fact that patient identity (and, in particular, indication for treatment) is not available, have been discussed elsewhere. [9,13,14] With no indication of use recorded in the PBS data, we were unable to identify whether prescriptions were being used for the treatment of hypertension. We have, however, considered this to be a reasonable assumption.

In addition, the dataset does not capture all prescriptions written. Thiazide diuretics, for example, cost less than the maximum patient contribution ($20.30 in 1999), and therefore, a patient without a concession card, would pay for these medications in full. As such, no claim for government subsidy would be made by a pharmacist and the prescription would, therefore, not be entered into the PBS database. Our analysis, therefore, would not have been undertaken on the full capture of prescriptions for general patients but did address all prescriptions for concession patients. Importantly, in assessing the limitations of the data used, there is no evidence that prescribing decisions for management of hypertension would differ between concessional and general patients.

Another limitation of the data used is that there may be changes in the amount of the patient copayment

Table 2. Regression model results for observed changes in prescribing

	Intercept	Trend	1st program	2nd program	3rd program	GPs	Auto-correlation	Residual SD
	α_0	α_1	β_1	β_2	β_3	γ	ϕ	
Mean rate								
Total antihypertensives								
Coefficient	4.081	0.002	0.000	0.004	−0.008	0.017	0.521	0.015
Standard error	0.009	0.000	0.002	0.001	0.003	0.007	0.088	0.015
p-value	0.000	0.001	0.806	0.006	0.010	0.018	0.000	0.015
	Combined *p*-value (β_1,β_2,β_3,γ) = 0.000							
Mean rate-thiazide & thiazide-like								
Coefficient	2.058	−0.001	−0.008	0.003	−0.004	0.009	0.838	0.022
Standard error	0.034	0.001	0.004	0.004	0.007	0.012	0.058	
p-value	0.000	0.621	0.017	0.496	0.567	0.443	0.000	
	Combined *p*-value (β_1,β_2,β_3,γ) = 0.002							
Mean rate low-dose thiazides								
Coefficient	0.068	−0.002	0.045	0.090	0.058	−0.006	0.726	0.041
Standard error	0.040	0.002	0.013	0.009	0.016	0.025	0.078	
p-value	0.091	0.131	0.001	0.000	0.000	0.794	0.000	
	Combined *p*-value (β_1,β_2,β_3,γ) = 0.000							
Mean rate beta blockers								
Coefficient	2.212	0.000	0.001	0.003	−0.010	0.000	0.471	0.017
Standard error	0.009	0.000	0.001	0.002	0.003	0.007	0.090	
p-value	0.000	0.626	0.328	0.070	0.001	0.974	0.000	
	Combined *p*-value (β_1,β_2,β_3,γ) = 0.000							
Mean proportion low-dose thiazides/all thiazides								
Coefficient	−2.048	−0.001	0.043	0.072	0.038	−0.008	0.853	0.037
Standard error	0.063	0.003	0.015	0.010	0.016	0.022	0.064	
p-value	0.000	0.762	0.004	0.020	0.019	0.700	0.000	
	Combined *p*-value (β_1,β_2,β_3,γ) = 0.000							

α_0 = intercept of model.
α_1 = the trend before the first intervention (that is, the underlying trend without NPS intervention).
β_1 = a term in the model that represents the first ''passive'' NPS intervention in October 1999.
β_2 = a term in the model that represents the second ''passive'' NPS intervention in September 2001.
β_3 = a term in the model that represents the third ''passive'' NPS intervention in August 2003.
γ = a term in the model for the number of GPs actively participating in the NPS hypertension program (cumulative monthly from Oct. 1999).
ϕ = autocorrelation of model errors.
Residual SD = Standard deviation of model residuals.

over time, which results in differential capture of individual drugs. For this reason, all drugs in this analysis were examined to ascertain whether there had been any changes in copayment status over the time of analysis. Several antihypertensives changed copayment status over the time period of study, including indapamide 2.5 mg, which changed from above to below copayment in November 1997 (i.e. prior to the period under study). None of the other thiazide diuretics changed copayment status.

The influence of indapamide (a thiazide-like diuretic) is difficult to understand and may have potentially complicated interpretation of the regression model. At the time of the first intervention, the low-dose formulation was unavailable and indeed the intervention message was to avoid the 2.5 mg high-dose preparation (as it had more adverse effects for no more antihypertensive efficacy at a higher dose). The listing on the PBS of the new low dose slow-release formulation (in November 2001—Fig. 8) coincided with a rapid rise in the proportion of low-dose thiazide to all thiazides, the proportion more than doubling in the 2 years after the first NPS intervention, and the data point at November 2001 showing a comparatively steeper increase in slope. New drugs (or new formulations) are often rapidly adopted in the first phase of release.[15,16] An interplay between the NPS program and the introduction of this new formulation may partly explain the increase in the use of low-dose thiazides.

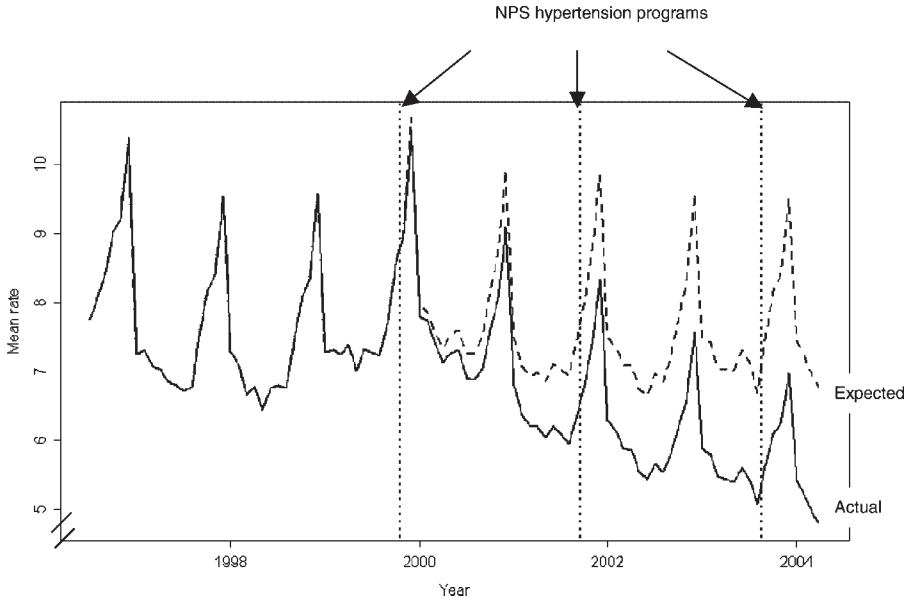

Figure 3. Mean prescribing rate of thiazide and thiazide-like diuretics—actual versus expected

Seasonality of prescribing is evident at the end of each calendar year (Figure 1). This effect is primarily due to patients becoming eligible for the 'safety net' (prescriptions reaching subsidy threshold) and also the stock-piling of medications under the scheme. The seasonal decomposition technique used in the analysis adjusted for this by removing the seasonality component and proceeding with linear regression modelling. The modelling technique used, assumes that the effect of the intervention is immediate and does not allow for any delay in effect. Similarly, the terms in the model associated with the interventions

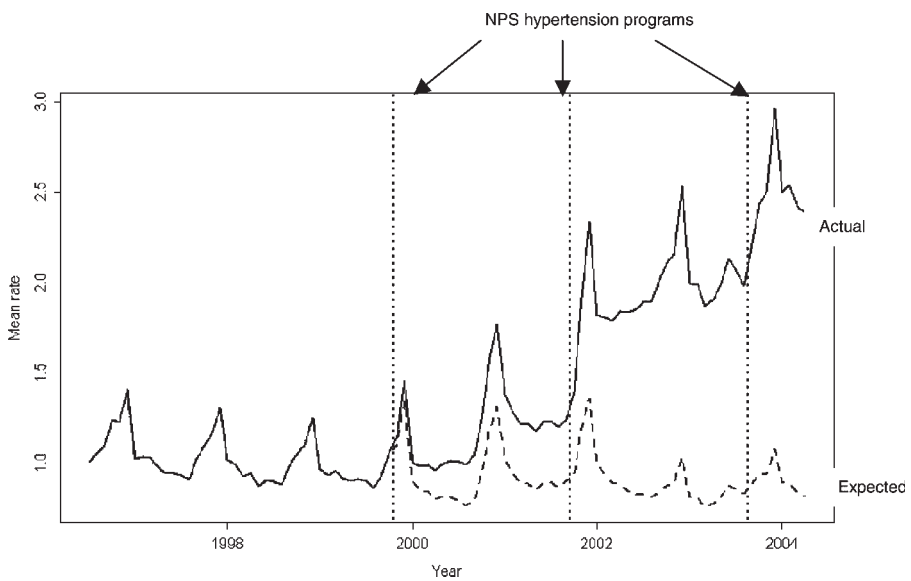

Figure 4. Mean prescribing rate of 'low-dose'thiazide and thiazide-like diuretics—actual versus expected

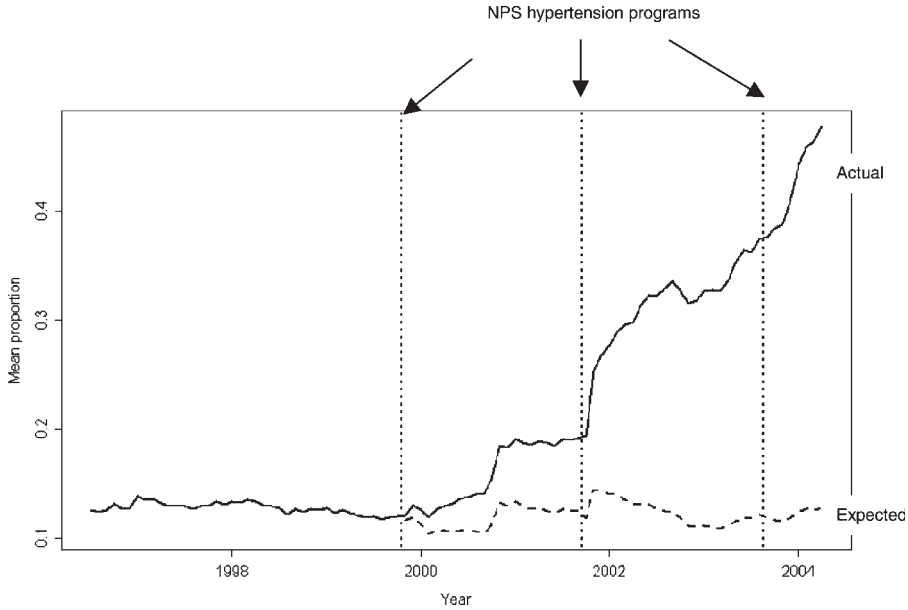

Figure 5. Low-dose thiazide and thiazide-like diuretics as proportion of all thiazide and thiazide-like—actual versus expected

are fixed at specific points in time and do not allow for the somewhat protracted roll-out of the active interventions. For example, clinical audits were undertaken by GPs from October 1999 until mid-2000, but the 'change point' is set at October 1999. Several regression models were trialled before the final version reported here. Other models trialled assumed that once a GP has changed prescribing behaviour, this change would be permanent. However, this does not reflect behaviour change theory in relation to the issue of sustainability and equivocal evidence from previous studies which aimed to

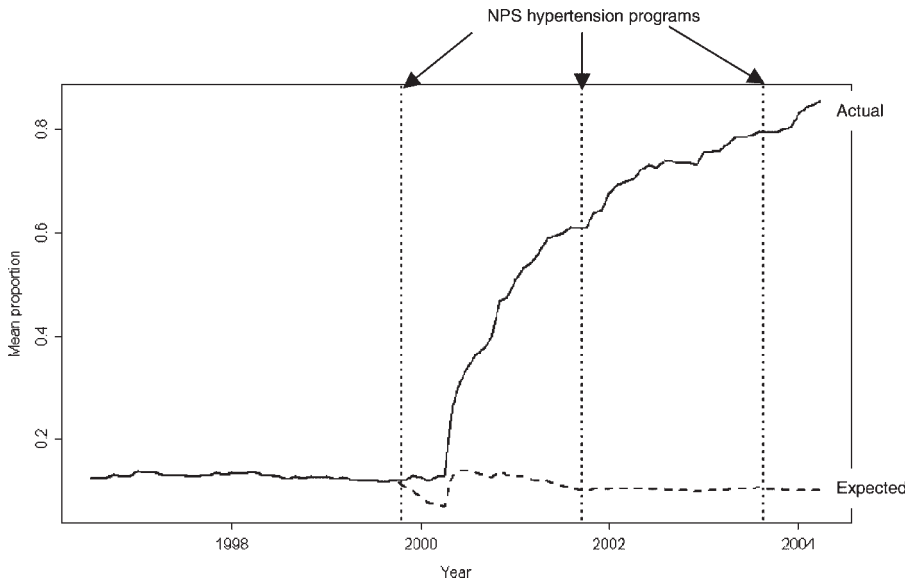

Figure 6. Low-dose thiazide and thiazide-like diuretics as proportion of all thiazide and thiazide-like plus combination products—actual versus expected

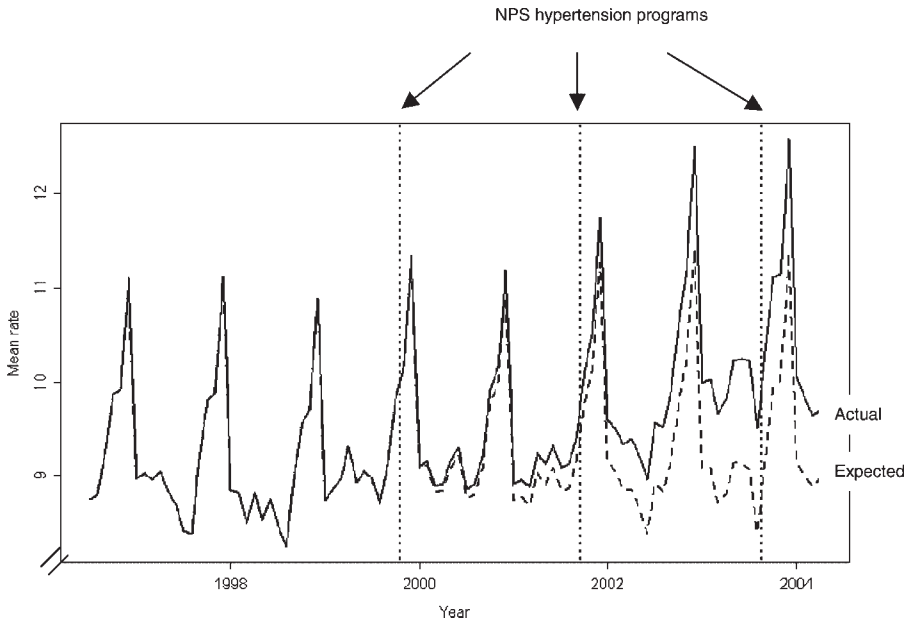

Figure 7. Mean prescribing rate of beta blockers—actual versus expected

influence prescribing[17,18]. This led to the decision to include decay terms in the model. Using low-dose thiazides as an example, a decay term estimated directly from the data as 0.021 specifies the rate at which the impact of the intervention is thought to dissipate. In this case, the intervention effect would take approximately 78 months to lose half its total effect, and about 182 months before 90% of its total

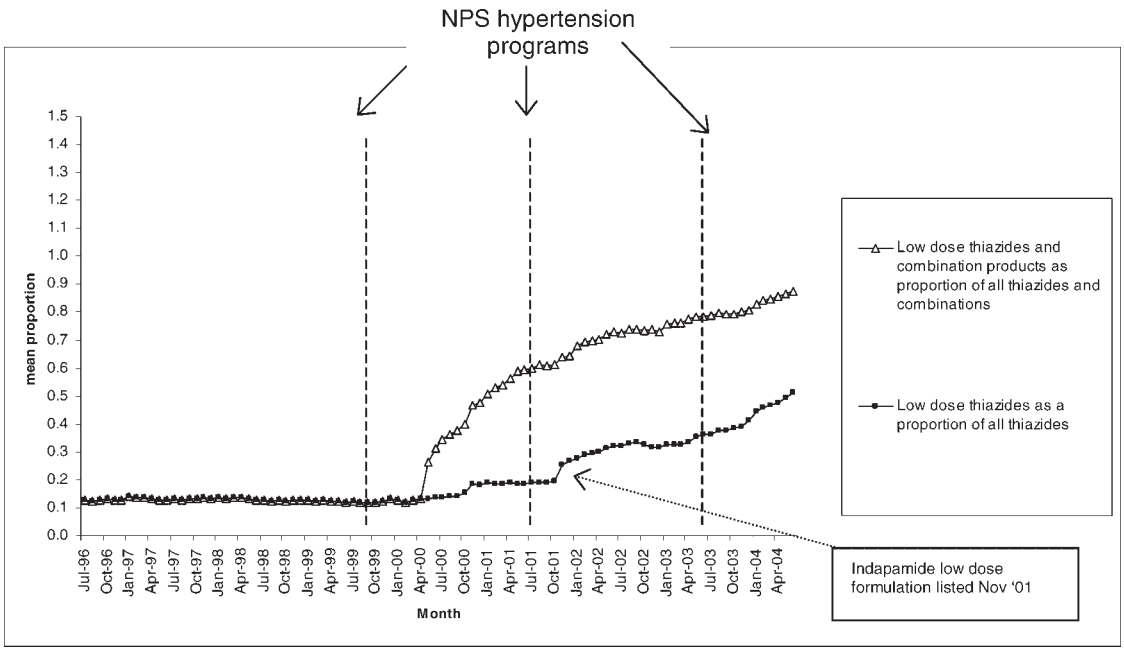

Figure 8. Mean proportion of low-dose thiazide diuretics as a proportion of all thiazides and as proportion of all thiazides plus combinations (per GP per month)

impact is lost. Despite the formal rigour of the regression modelling and attempts to allow for decay, there is no certainty that observed changes in slope are due solely to the interventions, since such models do not attempt to include all potential (and unknown) environmental variables, which might also influence the pattern of drug utilisation.

Our modelling did not show any significant results for the active GP term (γ). We had hoped that by including this as a separate term, we might have been able to measure the differential contribution of active (educational visiting, audit or case study) compared to passive (receipt and readership of print materials) participation.

The analysis does not address whether low-dose thiazides (or beta blockers) are being used as first-line therapy and ideally we would like to have been able to measure this directly. In addition, beta blocker use is confounded by their use in other cardiovascular conditions (although we did exclude beta-blockers primarily used for heart failure).

Several other environmental factors limit the attribution of causality to the NPS programs.

Heavy promotion by pharmaceutical companies at the release of new medications (or new formulations of existing medication) are known to influence prescribing and are difficult to measure and control for.[19] Approximately 6 months after the first intervention in October 1999, the first of the combination ACE/A2RAs plus a thiazide diuretic was listed for subsidy. Therefore, the observed decrease in thiazide use may have been partly due to the rapid uptake of these new products with patients being changed to a combined formulation. Analysing the total thiazide prescribing (thiazides plus combination products) is problematic as prescriptions for thiazides are usually for 3 months supply whereas the combination products contain only 1 month supply.

Release of large clinical trial results may also have had an influence: ALLHAT-2002[20], ANBP2-2003[21], WHO-ISH 1999 & 2003[4,22], and National Heart Foundation guidelines-1999[3], and late 2003.[23]

Despite the observed increase in prescribing of low-dose thiazides, from 1.1 per 1000 consultations in October 1999 to 2.4 per 1000 in October 2003, it should be noted that this equates to only 7 extra prescriptions per GP per year (knowing that a GP provides an average of 6000 consultations per year[24]) so the effect size is modest.

Previous studies and reviews suggest that an effect size of 5–10% is typical for a successful strategy to change prescribing behaviour.[25] Reminder systems and educational outreach are the most robust methods with moderate effects.[2] The evidence for educational materials, audit and feedback and patient-mediated interventions is weaker with fewer evaluations of those interventions. Multifaceted interventions are generally considered more effective than single interventions but there is no direct relationship between the number of interventions and the effect size. We are unable to ascertain which of our interventions had the most effect and both types of participation were given equal weighting. More importantly we are unable to determine whether any change in prescribing due to either type of intervention is sustainable.

Despite the analytic and environmental limitations discussed and an imperfect data source for measurement of effect, this study highlights the complexity and challenges of carrying out the evaluation of a national prescribing program. Multiple factors influence GP prescribing decisions and demonstrating causality in influencing prescribing is difficult. We have highlighted some of the challenges in this process and hope that with knowledge gained in the process we can build on these lessons to ensure continuing best practice in evaluation of future NPS programs.

KEY POINTS

- Interpretation of changes in drug utilisation patterns must also consider the complexity of the prescribing environment and, in particular, any changes in the marketing and promotion of any related drugs.
- The modelling of interventions should consider whether and to what extent decay of intervention impact might occur.
- Successive interventions with the same key messages directed at the same group of GPs cannot be regarded as independent events (especially when close in time) and thus a reliable statistical test should treat them as a group rather than as separate events (otherwise their collinearity may result in misleading non-significance for each intervention).
- The complexity of evaluating educational programs aimed at improving prescribing should be seen as a challenge worth pursuing and reporting, since there is limited quantitative information which supports such endeavours.

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APPENDIX

LIST OF DRUG NAMES

ACE inhibitors: captopril, enalapril, lisinopril, perindopril, ramipril, quinapril, cilazapril, fosinopril, trandolapril

ACE inhibitor in combination with thiazide diuretic: enalapril maleate with hydrochlorothiazide, perindopril with indapamide, quinapril with hydrochlorothiazide, fosinopril with hydrochlorothiazide

Angiotensin II receptor antagonists: candesartan, losartan, eprosartan, irbesartan, telmisartan

Angiotensin II receptor antagonists in combination with thiazide diuretic: irbesartan with hydrochlorothiazide, candesartan with hydrochlorothiazide, eprosartan with hydrochlorothiazide, telmisartan with hydrochlorothiazide

Beta blockers: alprenolol, oxprenolol, pindolol, propranolol, timolol maleate, metoprolol, atenolol, labetalol (bisoprolol and carvedilol excluded as use is primarily in heart failure)

Calcium channel blockers: amlodipine, felodipine, nifedipine, lercanidipine hydrochloride, mibefradil, verapamil, diltiazem

Thiazide & thiazide-like diuretics: bendrofluazide, hydrochlorothiazide, chlorothiazide, methyclothiazide, chlorthalidone, metolazone, indapamide, hydrochlorothiazide with triamterene, hydrochlorothiazide with amiloride hydrochloride

Low-dose thiazide and thiazide-like: hydrochlorothiazide 25 mg, chlorthalidone 25 mg, indapamide 1.5 mg (sustained release), hydrochlorothiazide with triamterene 25 mg/50 mg

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