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Effectiveness, safety and cost of drug substitution in hypertension

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Cost-containment measures in healthcare provision include the implementation of therapeutic and generic drug substitution strategies in patients whose condition is already well controlled with pharmacotherapy. Treatment for hypertension is frequently targeted for such measures. However, drug acquisition costs are only part of the cost-effectiveness equation, and a variety of other factors need to be taken into account when assessing the impact of switching antihypertensives. From the clinical perspective, considerations include maintenance of an appropriate medication dose during the switching process; drug equivalence in terms of clinical effectiveness; and safety issues, including the diverse adverse-event profiles of available alternative drugs, differences in the 'inactive' components of drug formulations and the quality of generic formulations. Patients' adherence to and persistence with therapy may be negatively influenced by switching, which will also impact on treatment effectiveness. From the economic perspective, the costs that are likely to be incurred by switching antihypertensives include those for additional clinic visits and laboratory tests, and for hospitalization if required to address problems arising from adverse events or poorly controlled hypertension. Indirect costs and the impact on patients' quality of life also require assessment. Substitution strategies for antihypertensives have not been tested in large outcome trials and there is little available clinical or economic evidence on which to base decisions to switch drugs. Although the cost of treatment should always be considered, careful assessment of the human and economic costs and benefits of antihypertensive drug substitution is required before this practice is recommended.

Introduction

Hypertension is one of the strongest modifiable risk factors for cardiovascular and kidney disease and has been identified as the leading risk factor for mortality [1]. In 2000, hypertension was estimated to affect almost 1 billion patients worldwide and its prevalence is predicted to increase by approximately 60% by 2025 [2]. In European countries the prevalence of hypertension in adults is estimated to be approximately 44% [3]. Given the increasing prevalence of hypertension and the continually rising expense of its treatment, measures that influence prescribing patterns could have a considerable impact on health expenditure.

Cost-containment measures in healthcare provision include drug switches without medical reason in patients whose condition is already well controlled with pharmacotherapy. This may take the form of therapeutic substitution, which encompasses switching within a drug class (i.e. the chemical entities are different but the main therapeutic mechanism of action is the same) or between classes (i.e. the active chemical entities and mechanisms of action are different). Patients may also be switched from a branded drug to a generic version (i.e. the active chemical entity is the same and the generic meets the criteria for bioequivalence with the original branded version). In some countries, such as the USA and Canada, switching can be performed by the pharmacist, without consulting the prescribing clinician or the patient. Such approaches are the subject of considerable debate, and several professional bodies (e.g. the American Medical Association [4], the American College of Cardiology and the American Heart Association [5]) oppose therapeutic substitution without prior authorization by the prescribing physician.

Switching of drugs is increasingly being mandated by the implementation of local or national healthcare cost-containment policies. In the UK, the Department of Health is currently consulting on the implementation of generic

substitution in the English primary care system [6]. The prescribing doctor will need to indicate actively that a branded drug should not be substituted, otherwise a generic will be dispensed where possible. This approach is already in place in many countries including the USA and Canada [7]. A tactic widely used in the USA is to implement 'step therapy' programmes, based on grouping drugs into tiers by cost [8, 9]. Drugs in the second tier (usually branded drugs) are only covered by the healthcare plan if drugs in the first tier (usually generics) have been prescribed but found unsuitable for the patient. A second-tier drug may be dispensed if the patient provides a co-payment or if specifically requested by the prescribing doctor. Other approaches that are likely to require medically unnecessary drug switching include 'reference drug' programmes, which permit reimbursement up to the cost of a preferred drug, and mandatory therapeutic substitution, which requires patients to switch to the cheapest medication in a class [8, 10]. With all of these approaches it is assumed that cost savings will be made when these policies are implemented.

In practice, a careful assessment of the potential benefits and costs of drug substitution should be applied. However, the full clinical and economic implications of drug switches are unknown and this may not be appreciated or considered by those implementing the switch. Cost-effectiveness analyses of such approaches rarely take into account costs other than drug acquisition costs and assume equal effectiveness without adverse effects, but without evidence [11–13].

The aim of this review is to highlight the potential clinical and economic implications associated with switching medications solely for cost-containment purposes in patients whose condition is already controlled with pharmacotherapy. These issues are illustrated with examples from the treatment of hypertension, particularly the renin–angiotensin system antihypertensives, angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs). From the clinical perspective we aimed to examine any potential means by which switching to a generic drug, a drug in the same class or a drug in another class might compromise the effectiveness and safety of antihypertensive therapy. From the economic perspective, we examined possible causes of additional healthcare resource use and how the cost-effectiveness of therapy could be affected by medication switching.

Methods

This qualitative review was based on literature searches conducted using PubMed to identify English language articles on switching antihypertensives and on switching medications in general. Reference lists of identified articles, including previous relevant systematic and qualitative reviews, were also examined for additional relevant studies and information. The review includes evaluation of information on: resource use and costs associated with switching, patient adherence and persistence with antihypertensives, patient satisfaction with switching, efficacy and safety aspects of ARBs and ACEIs, drug formulation differences, and guidelines for switching antihypertensives. Searches were conducted on PubMed and were generally limited to recent publications (previous 10 years). Search terms included combinations of the following: (*angiotensin* OR *hypertension* OR *antihypertensive*), (*switch* OR *interchange* OR *conversion* OR *substitution* OR *generic*), (*adherence* OR *persistence* OR *compliance* OR *discontinuation*), (*cost* OR *economic* OR *pharmacoeconomic*), (*perception* OR *attitude* OR *satisfaction*), *formulation*, *guidelines*, *generic*.

Switching antihypertensives: are clinical effectiveness and safety maintained?

Implementing switching

At present, the guidance for physicians and pharmacists on switching antihypertensives is poor. There is little information on equivalent doses or guidance to ensure that blood pressure control is maintained following drug substitution, although health authorities may provide some guidance [14]. Concerns have also been raised with regard to switching between statins. A study of patients switching from atorvastatin to simvastatin found that a lower therapeutic dose was prescribed in 38% of the switches made, which could potentially have an adverse effect on patients' health [15].

In the absence of clear guidance, and given the substantial within-patient variation in response to antihypertensive drug classes [16], when a switch is made, the new drug is likely to be initially administered at a low dose and titrated upwards. A delay can thus occur in regaining hypertension control, which could impact on clinical outcomes in patients at high cardiovascular risk. Even short periods of uncontrolled hypertension can lead to an increased risk of major cardiovascular events. This was demonstrated in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial in which subjects with inadequate blood pressure control for a few weeks or months had a higher risk of stroke, myocardial infarction and death compared with those who had adequately controlled blood pressure [17]. A randomized study in primary care has reported better blood pressure control in the first 3 months of antihypertensive treatment when a stepwise add-on approach was used compared with an approach allowing drug switching [18], suggesting that switching may delay achieving control. Health professionals have expressed concern regarding switches made for nonmedical reasons in patients with hypertension [19]. Table 1 illustrates the potential differences and lack of evidence that may accompany a switch from a branded ARB to possible alternatives, this being a switch likely to be considered for economic reasons in clinical practice in the future.

Table 1

Illustration of similarities and possible differences between a reference branded ARB and potential alternatives

Aspect of branded ARB	Generic ARB*	Any other ARB	Any ACEIs
Main mechanism of action	≡	≡	≠
Structure of drug	≡	≠	≠
Excipients and binders	≠	≠	≠
Appearance	≠	≠	≠
Pharmacokinetics			
In healthy subjects	≡	NR	NR
In patients	?	NR	NR
In special populations	?	NR	NR
Evidence for similar efficacy			
Primary outcome (surrogate marker)	?	?	?
Clinical cardiovascular outcomes	?	≠	≠
In same clinical indications	?	≠	≠
Pleiotropic effects	?	≠	≠
Safety			
Adverse events	?	≠	≠
Drug–drug interactions	?	≠	≠
Contraindications and warnings	≡	≠	≠
Adherence and persistence	≠	≠	≠

*No generic ARBs are currently available; based on evidence usually available for an approved generic version of a drug. ≡, equivalent, ≠, not equivalent, ?, equivalence may not be proved or evidence suggests differences may occur. ACEI, angiotensin-converting enzyme inhibitor, ARB, angiotensin receptor blocker, NR, not relevant.

Evidence-based medicine and switching

A factor that should be considered for both between- and within-class switching is the level of available evidence for the safety and effectiveness of individual drug formulations. This is particularly important when considering the patient's comorbidities and risk factors because individual drugs, even within the same class, can have different licensed indications. In addition, trial data may be limited to surrogate markers, i.e. blood pressure, rather than clinical outcomes. Although drugs may have a similar effect on surrogate markers for a medical condition, it should not be assumed that the clinical outcomes will also be similar. For example, analysis of subjects receiving monotherapy in the VALUE study revealed a significantly lower incidence of heart failure in the valsartan-treated group than in the amlodipine-treated group, despite similar blood pressure reductions [20]. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study demonstrated that in patients with essential hypertension and left ventricular hypertrophy, treatment with losartan prevented significantly more cardiovascular morbidity and mortality than atenolol, despite similar lowering of blood pressure [21]. Likewise, in the Anglo-Scandinavian Cardiac Outcomes Trial - Blood Pressure Lowering Arm (ASCOT-BPLA), greater differences in the incidence of cardiovascular outcomes were observed between the groups receiving amlodipine and atenolol than would be expected from the small between-treatment difference that was observed in systolic blood pressure [22].

Substitution strategies have not been tested in large outcome studies in hypertension, except those switches dictated by the emergence of adverse effects. Such studies have generally used stepwise add-on drug strategies. Virtually all the hypertension outcome trials that showed the benefits of drug-induced blood pressure reduction in terms of cardiovascular event prevention (HOT [23], ALLHAT [24], LIFE [21], VALUE [17], ASCOT [22], ONTARGET [25], etc.) have used strict stepwise upward-titration drug treatment regimens, and substitution was only allowed in the event of adverse effects. Thus the efficacy and safety of the practice of substitution in the absence of adverse effects has never been thoroughly studied in large trials.

Considerations specific to the different types of drug switching will be discussed below.

Drug formulation considerations

Even within a class, drugs vary in a multitude of aspects. Even subtle differences in the structure of active ingredients, drug formulation, interventions to modify (prolong) the duration of drug action, and the 'inactive' ingredients can lead to differences in activity and pharmacokinetics and, hence, side effects. For example, a study of rifampicin powders produced by different manufacturers found that the crystal form of the drug varied among manufacturers and between batches from the same manufacturer [26]. These disparities caused differences in the dissolution rate and hence could affect drug bioavailability.

Formulation and excipient differences may also introduce unexpected adverse effects, e.g. allergic reactions [27] or interactions with other drugs. Differences in gluten or lactose content could, e.g. alter gut motility in some patients, while substituted drugs may introduce additives with allergenic potential [27]. Although excipients such as polysorbate 80 and polyoxyethylated castor oil are considered inert, there are examples of altered drug metabolism with such compounds [28, 29]. In addition, differences in their elimination could affect drug disposition [30]. The true impact of these factors on patients' care in general practice with regard to the incidence of unexpected events is unknown and difficult to quantify.

Switching between different drug classes

A common form of drug substitution in the treatment of hypertension is to switch between ARBs and ACEIs. These drug classes are widely regarded as being therapeutically equivalent in terms of reducing blood pressure. For certain drugs in defined patient populations, clinical outcomes have also been shown to be similar. For example, the large ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) demonstrated that telmisartan 80 mg was equivalent to ramipril 10 mg in reducing the incidence of cardiovascular events in patients with vascular disease or high-risk diabetes, without heart failure [25]. However, equivalence between any ARB and any ACEI has not been proved. The UK's National Institute

for Health and Clinical Excellence states that 'they should be treated as equal in terms of efficacy', although the basis for this decision is not clear [31]. The USA's Agency of Healthcare Research and Quality (AHRQ) concluded that ACEIs and ARBs have similar long-term effects on blood pressure, a surrogate marker for clinical outcomes, in patients with essential hypertension, but also noted that there is insufficient evidence to determine equivalence between ACEIs and ARBs with respect to mortality, major cardiovascular events or quality of life outcomes [32].

When switching between drugs, physicians need to consider the individual patient's comorbidities and the most suitable drug. Some guidelines specify that switching should not occur in patients with certain comorbidities. For example, some state that patients with heart failure, diabetes mellitus or diabetic nephropathy should not be switched from an ARB [14].

Other evidence suggests that there are differences in effectiveness between ARBs and ACEIs. Crossover studies have demonstrated that individual patients respond differently to drugs in the two classes [33–36]. For example, a study in patients with essential hypertension found that although there was a significant correlation between responses to lisinopril and telmisartan ($r = 0.77$, $P < 0.001$), 19% of patients showed a difference between the two drugs in their systolic blood pressure response and 25% showed a difference in their diastolic blood pressure response [36]. Similar results were seen in a study comparing responses to candesartan and lisinopril in patients with essential hypertension: while 50% of patients responded to both drugs and 16% to neither, 20% responded to the ACEI but not the ARB and 15% responded to the ARB but not the ACEI [34].

So-called 'pleiotropic' effects differ between the drug classes and may confer particular advantages. There is evidence that the ARBs and/or ACEIs may be associated with antiatherogenic, antioxidant, antidiabetic, antiplatelet and atrial antifibrillatory effects [37, 38] and valsartan, in particular, may be associated with improvements in cognitive function [39]. In reviewing potential effects on clinical outcomes other than hypertension, the AHRQ concluded that there were no consistent differences between ACEIs and ARBs with regard to lipid concentrations, progression to type 2 diabetes mellitus, markers of carbohydrate metabolism/diabetes control, left ventricular mass or renal disease progression [32].

Safety issues may preclude switching between the ARB and ACEI classes. Persistent dry cough is common with ACEIs, occurring in up to 20% of patients, and is a frequent cause of medication discontinuation [25, 32, 40, 41]. By contrast, treatment with ARBs has not been associated with cough [42]. In addition, ACEIs are associated with angioedema. Although the incidence is thought to be low (0.1–0.2% [25, 43–46]), higher rates have been reported [47, 48]. The risk of experiencing angioedema is considerably lower with ARBs [25, 49–54]. The European Society of Hypertension and European Society of Cardiology included angioneurotic oedema as a contraindication to the use of ACEIs but not ARBs [55].

Class-specific drug–drug interactions need to be taken into account when considering a drug switch. There are few differences between ARBs and ACEIs with regard to potential drug–drug interactions [56]. However, absorption of ACEIs is possibly reduced by antacids, and ACEIs may enhance the hypoglycaemic effect of insulin, sulphonylureas and metformin. ARBs may increase the blood concentration of lithium. Contraindications and warnings will vary between drugs of different classes. An important difference between ARBs and ACEIs is that, unlike ARBs, ACEIs are predominantly excreted by glomerular filtration. Great caution is thus required when switching patients with renal insufficiency from ARBs to ACEIs [41, 57].

Another aspect to consider is patient compliance with therapy. Adherence to and persistence with antihypertensives are acknowledged to be poor [58, 59]. This is an important issue when treating hypertension: several studies have shown that poor adherence to and persistence with antihypertensives lead to suboptimal blood pressure control and hence reduced cardiovascular protection [60–65]. Thus, when considering making a switch it is worth taking into account that patient persistence with therapy in clinical practice has repeatedly been shown to be better with ARBs than with ACEIs [32, 66–69].This was clearly evident in the ONTARGET study in which patients randomized to receive an ARB had a significantly lower rate of discontinuation due to adverse events, such as cough and angioedema, compared with those receiving an ACEI, despite the fact that patients with intolerance to ACEIs had been excluded from the study [25].

Within-class substitutions

Therapeutic substitution may also take the form of switching between drugs in the same class. As head-to-head comparisons are not always performed, there may be a tendency to extrapolate efficacy data from biomarkers between drugs within the same class (i.e. to assume 'class effects'). However, even within a class there may be important differences in structure, therapeutic and adverse actions and interactions [70]. An example of how switching between drugs within a class can have a detrimental clinical effect comes from an observational database study of patients who were switched from atorvastatin to simvastatin [71]. The risk of death or first major cardiovascular event was significantly associated with switching compared with matched controls who did not switch (hazard ratio 1.30, 95% confidence interval [CI] 1.02, 1.64) [71].

Furberg & Psaty have discussed the potential problems that may arise through extrapolating proof of efficacy between drugs within a class [72]. Taking ACEIs as an example, the authors noted that of the 10 marketed ACEIs approved by the US Food and Drug Administration (FDA) for the treatment of hypertension, five had not been

shown to reduce mortality/morbidity for any indication. Three of the ACEIs were approved for indications such as left ventricular dysfunction/heart failure after myocardial infarction on the basis of improvements in surrogate endpoints rather than outcome data. The authors also highlighted the fact that trials using surrogate endpoints are not of sufficient duration to prove long-term safety.

Differences in clinical outcomes between individual drugs do need to be considered. Although some meta-analyses have found no difference between ARBs with respect to blood pressure lowering [73, 74], others have noted significant differences [75]. Drug indications may differ based on clinical evidence. For example, valsartan is indicated for postmyocardial infarction left ventricular failure and left ventricular dysfunction, for which other ARBs, such as losartan, are not indicated. Similarly, in the ARB class only losartan and irbesartan are indicated for patients with diabetic nephropathy.

Structural differences between drugs within a class may lead to drug-specific beneficial or adverse effects. There are no clear distinctions between the different ARBs in terms of pleiotropic effects. However, there are some interesting reports of possible differences, including effects on insulin sensitivity, C-reactive protein, arterial stiffness, atrial fibrillation and superoxide dismutase expression [76–80]. At present, the clinical relevance of these observations remains to be proved.

Drug–drug interaction profiles vary between members of a drug class. ARBs have a low potential for drug–drug interactions compared with other antihypertensives. However, variations within the class have been detected, mainly due to differing affinities for cytochrome P450 (CYP) isoenzymes. For example, losartan is converted to its active metabolite by CYP2C9 and CYP3A4 [81, 82] and thus has the potential to interact with drugs such as fluconazole and rifampicin [83, 84]. By contrast, other ARBs such as valsartan are not metabolized by cytochrome P450 [85] and therefore drug–drug interaction at the level of liver enzyme-mediated metabolism is unlikely.

Clearly, equivalent efficacy and safety should not be assumed even for drugs within the same class. Rather, the physician needs to base prescribing decisions on the clinical outcome evidence for the particular drug.

Generic substitution

The general perception among physicians is that an approved generic version of a drug is identical to the branded original and can be prescribed without further consideration. However, for marketing approval, a generic drug only needs to demonstrate equivalent average pharmacokinetic properties to the originator drug. Neither proof of safety nor equivalent efficacy for a clinical endpoint(s) are required by the FDA or the European Agency for the Evaluation of Medicinal Products. For 'equivalence', the mean ratio of key pharmacokinetic parameters (maximum plasma concentration and area under the concentration–time curve) of the generic drug must have a 90% CI within 0.80 and 1.25 of the original – i.e. in percentage terms, the average deviation must be within 80–125% of the original, although narrower ranges may apply in some instances. Required bioequivalence studies generally do not reflect the target patient population: such studies are conducted in healthy subjects aged 18–55 years; patient-related variables and age- and disease-related (e.g. renal insufficiency) factors are not considered. In addition, as only single-dose studies are generally required, the cumulative effects of dosing are not assessed. Lack of bioequivalence is a particularly important issue for drugs with a narrow therapeutic index, such as antiarrhythmics [86].

Many physicians may be unaware of the variation in bioavailability permitted by regulatory bodies. A survey conducted in the USA found that only 17% of physicians correctly identified the FDA's standards for drug bioequivalence [87]. Based on these findings, Kirking and colleagues concluded that '. . . many physicians are making decisions regarding generic products on the basis of inaccurate perceptions and beliefs that assume more rigid standards for bioequivalence than [the] FDA generally requires' [88].

Formulation differences also occur between the original branded drug and the generic version. The authorities do not require the 'inactive' ingredients in a generic formulation to be identical to those in the branded original. Impurities or small changes in the formulation or excipients can alter medication properties and introduce unexpected effects that affect drug efficacy and safety (e.g. in duration of action, interactions with other drugs and patients' reaction to the drugs) [89]. Formulation differences have been noted in generic versions of antihypertensives [90–92]. For example, a study of enalapril formulations found considerable variation in the stability of different preparations, leading to substantial differences in drug concentration and drug-release profiles between the reference and generic formulations [90]. Packaging too can influence a drug formulation's stability: e.g. losartan/hydrochlorothiazide tablets have been shown to be sensitive to moisture and adequate packaging must be used to counter this [93]. Excessive levels of impurities have been found in generic formulations of a range of different drugs [91, 94–96].

A study of generic switching, covering 15 different drugs in Sweden, reported that increasing generic market share was associated with an increase in the number of adverse effects reported, suggesting that closer examination of the consequences of generic substitution is required [97]. Patients and physicians frequently express concern about generic formulations and, in some cases at least, it seems that these concerns are not unfounded. The FDA recently banned Ranbaxy Laboratories, a pharmaceutical company specializing in generics, from importing 30 generic versions of drugs from India into the USA on the basis of poor quality [98].

The effect of switching on patient behaviour

As discussed above, patients' adherence to their antihypertensive treatment regimen is essential for optimal clinical outcomes. There are many factors associated with switching that might reduce a patient's compliance and these should be taken into account when considering implementing a switch for nonmedical reasons. Even the effect of changing product packaging and tablet appearance should be considered as this can cause confusion, particularly in the elderly [99].

Patients are particularly wary of generics, often considering them to be inferior to the branded versions [100]. This attitude is influenced by the patient's perception of the severity of the condition to be treated. A US survey of consumers' opinions found that using generics to treat conditions such as hypertension or 'heart problems' was considered to be riskier than using them to treat pain or a cough [101]. This and other studies found that many patients would refuse to switch to generics, regardless of personal cost savings [101, 102].

A survey conducted in the USA for the National Consumers League revealed that consumers had significant concerns about therapeutic substitution [103]. Notably, 70% of prescription users stated that they would be very or extremely concerned if their prescription was changed without their doctor's knowledge or consent and 22% said that this concern would persist even if their doctor consented to the switch. In patients who experienced therapeutic switching, 40% said that the new drug was not as effective, 30% said they experienced more side effects, and 47% were dissatisfied with the process. As with generic switching, patients' opinions of therapeutic substitution were influenced by the severity of the condition. For a chronic condition with significant potential health implications, less than 23% of patients said that they would be likely to consider a therapeutic substitution.

It has been suggested that concerns about switching may cause a nocebo effect [100, 104], i.e. patients' negative expectations lead to negative outcomes. Many investigators also report that therapeutic substitution results in increased reporting of adverse events or negative experiences [19, 102, 105]. In a UK study of primary care patients' responses to the application of a generic formulary to their repeat prescriptions, 46% stated that they were dissatisfied with the change in prescribing [105]. Within 4 months of the formulary being implemented, 20% of patients had switched back to their original drug. A key cause of dissatisfaction seemed to be that patients felt impotent if they perceived that a change had been forced on them.

It has been reported that generic substitution *per se* does not adversely affect patient adherence [106]. However, a survey of enrollees in managed care organizations in the USA found that respondents generally agreed that generic substitution affected their adherence to their medications [107]. Several investigators have demonstrated that patients' adherence to and persistence with treatment are reduced following switching of antihypertensive drugs [108–111]. For example, in a study of antihypertensive therapy, 'therapeutic turbulence' (a switch to one or more drugs, addition of a new drug, or dropping of one or more drugs) reduced patients' persistence [108]. Patients with one change within 6 months of the index prescription for an antihypertensive drug were found to be at greater risk of not persisting than patients without any drug changes (risk ratio [RR] 1.07, 95% CI 0.94, 1.22). Patients experiencing two or more changes in the first 6 months were at even greater risk of not persisting (RR 1.25, 95% CI 1.12, 1.37). This difference was statistically significant ($P < 0.05$) and remained so for the first 3 years of observation.

Similar findings have also been reported regarding treatment with statins. Patients who switched statins were significantly less compliant and significantly more likely to discontinue than those not switching [71, 112].

It is clear that improved communication with the patient is essential to increase the likelihood of successfully switching drugs [102, 113].

Impact on resource use and costs

Medication switching is a cost-containment strategy only if the potential savings from switching outweigh the costs of healthcare resources required for the switch. Undoubtedly, drug acquisition costs are likely to be lowered by implementing switching, but these costs represent only a small part of the total treatment cost. In the USA, 'medical durables', including prescribed medications, were estimated to represent 11% of the total direct and indirect costs of cardiovascular disease, and 35% of the total cost of hypertension in 2009 [114]. In the European Union, medications were estimated to account for just 16.8% of the costs of cardiovascular disease in 2003 [115].

Drug acquisition costs are not the only type of cost affected when drug switching is implemented. As discussed above, switching can result in poorer adherence and persistence, increased adverse-event reporting and reduced effectiveness. A less expensive antihypertensive agent that causes health problems that need to be treated, e.g. diabetes caused by β-adrenoceptor blockers, could increase costs [116]. Conversely, a more expensive choice of antihypertensive drug that relieves comorbid clinical problems, e.g. an ARB could delay the progression to end-stage renal disease in patients with diabetic nephropathy, may help reduce costs overall [117]. Costs incurred either in the process of switching or as a consequence of switching are thus likely to include those for administration, additional clinic visits, extra laboratory tests and possibly hospitalization due to the patient's

Table 2

Examples of short- and long-term resource use and costs identified as being associated with switching antihypertensives, in addition to drug acquisition costs

Resource type	Resource use or average direct cost[a] (time period after switch)	Year of pricing[b]	Reference
Short-term resource use associated with switch implementation			
Clinic visit	1.24 × US$52.33[c]	(1989)	[122]
	1 × US$28.00	(1989/1990)	[123]
	2 × €7.05 (US$8.64)[d]	2004	[129]
	£3.70[e] (US$6.73)[d]	2005	[130]
Laboratory tests	US$4.55	(1989)	[122]
	US$0.00	(1989/1990)	[123]
	€39.12 (US$47.92)[d]	2004	[129]
Pharmacy			
Prescription filling time	US$0.23	(1989)	[122]
Setting up programme	US$1020 (fixed)	(1989/1990)	[123]
Adverse reactions			
Telephone contact	US$0.17[f]	(1989)	[122]
Discarded medication	US$0.95	(1989/1990)	[123]
Office visit	US$3.21	(1989/1990)	[123]
Drug wastage	US$9.05	(1989)	[122]
Explaining switch to patients	US$1.40[f]	(1989/1990)	[123]
	£0.32[g] (US$0.39)[d]	(2005)	[130]
Indirect costs	NA		
Long-term resource use arising from switching antihypertensives			
Clinic visits	£5 (US$7.50)[d] increase in cost *vs.* nonswitchers (1 year)	(1992–1994)	[121]
	US$115 ($28 per visit)[h] (1 year)	2000	[120]
	11% increase in visits, CA$13 (US$9.49)[d] increase in cost *vs.* nonswitchers[i] (2 months)	(1996/1997)	[127]
	18% increase in visits, CA$13 (US$9.49)[d] increase in cost *vs.* nonswitchers[i] (2 months)	(1996/1997)	[128]
	66–78% increase in visits, US$37 increase in cost *vs.* nonswitchers (1 year)	2002	[124]
Laboratory/diagnostic tests	US$31[h] (1 year)	2000	[120]
Outpatient visits	35–41% increase in outpatient visits, US$20 increase in cost *vs.* nonswitchers (1 year)	2002	[124]
	US$177 increase in cost *vs.* pre-switch (6 months)	(2000–2002)	[125]
Hospitalization	£24 (US$36)[d] increase in cost *vs.* nonswitchers (1 year)	(1992–1994)	[121]
	No significant excess in admissions *vs.* nonswitchers (2 months)	(1996/1997)	[127]
	No significant excess in admissions *vs.* nonswitchers (2 months)	(1996/1997)	[128]
	37–42% increase in inpatient visits, US$162–185 increase in cost *vs.* nonswitchers (1 year)	2002	[124]
Emergency room visits	US$4[h] (1 year)	2000	[120]
Long-term care	No significant excess in admissions *vs.* nonswitchers (2 months)	(1996/1997)	[127]
	No significant excess in admissions *vs.* nonswitchers (2 months)	(1996/1997)	[128]
Medication	Increase of US$28 compared with pre-switch, co-payment increased by US$9 (6 months)	(2000–2002)	[125]
Indirect costs	NA		

[a]Cost given per patient unless otherwise stated. [b]Where year of pricing is not stated, the years covered by the study are given in brackets. [c]The authors estimated that 24% of patients would require a second visit to adjust dosage. [d]Approximate value, based on historical exchange rate. [e]Includes time spent by general practitioner (£2.77) and time for repeat blood pressure measurements (£0.93). [f]Pharmacist's time. [g]Postage costs. [h]No control (nonswitchers) group. [i]Costs not specified but 'reflected increased number of visits to physicians'. NA, no information available.

condition not being adequately controlled by the substituted drug (e.g. for cardiovascular events associated with suboptimal blood pressure control [17]). As economic modelling should consider all possible incurred costs and should ideally be conducted from the societal perspective [118], indirect costs should also be considered, including those associated with lost productivity [119] and informal care [115].

Potential additional resource use associated with switching antihypertensives has been investigated by several investigators [109, 120–130] and switching was found to incur direct costs. For example, a retrospective analysis of patients who received ARBs found that those who switched between ARBs incurred significantly higher annual all-cause medical costs than those who did not switch ($6286 *vs.* $5701, respectively, $P < 0.001$) [109]. Table 2 illustrates the types of resource identified as being used in the process of switching antihypertensives (i.e. for performing the switch) or soon after, and those used in the longer term (months or years) after such a switch, potentially due to poor blood pressure control. For example, Lindgren-Furmaga and colleagues investigated the short-term costs associated with switching from enalapril to lisinopril [122]. At least one follow-up visit was required, with 24% of patients requiring a second visit. Laboratory tests, drug wastage, pharmacists' time and telephone contact with patients were also identified as sources of additional cost. In total, the direct short-term cost associated with switching was $66.33 per patient. Based on this cost-analysis, and not taking into account any longer-term costs

that might be incurred, the authors calculated that it would take up to 17 months for the reduced drug acquisition costs to mitigate the costs associated with the switch. In the longer term, additional healthcare resources could be required, such as hospitalization and emergency room visits, because of poorly controlled hypertension. Murawski & Abdelgawad looked at costs incurred in the year following switches due to implementation of a preferred drug list for ARBs, ACEIs and calcium-channel blockers (CCBs) [124]. The authors noted substantial increases in the numbers of clinic, hospital inpatient and outpatient visits in the population that switched compared with a control population (Table 2). Based on these events alone, and not including the costs of implementing the programme, the authors calculated that an additional annual cost would be incurred of $219–242 per patient who switched antihypertensive drug as part of the preferred drug list programme (2002 costs). Similarly, although some studies of statin switching have found no additional costs incurred through switching [131], others have noted increased resource use and costs incurred through additional clinic visits, laboratory tests, and laboratory technician and pharmacist time [132–135]. It is important to note that such costs have not always been included in economic evaluations of switching programmes.

Of the resource types investigated in studies of antihypertensive switching, additional clinic visits are a key cost driver. These are likely to be required for a variety of reasons including increased communication with patients to explain and reassure them about the switch. A UK study of primary care patients' responses to switching to a generic formulary found that for every 100 intended prescription changes, 16 additional consultations were generated [105]. Therapeutic switching is also likely to involve dose titration of the new drug. For example, a study of switching from CCBs to amlodipine/benazepril noted that 44% of patients required one dose titration and 16% required two [120]. Additional physician or hospital visits may be required to address treatment failure or new adverse events after the switch [124]. Finally, patients sometimes switch back to their original drug, generating further rounds of clinic visits [19, 105, 130, 136].

The potential impact of poor compliance with therapy is not often taken into account in cost-effectiveness analyses [137]. However, several studies have highlighted the additional resource use and costs incurred by poor adherence to antihypertensives [64, 136–144]. Greater compliance with antihypertensive therapy has been shown to be associated with lower costs for physician, hospital and laboratory services [140, 143]. In particular, several investigators have noted that the risk of hospitalization, and hence hospitalization costs, increases with poorer adherence to and persistence with antihypertensive therapy [64, 65, 139]. Little is known about the effect on indirect costs of antihypertensive treatment adherence and persistence. However, Rizzo and colleagues estimated that a person with uncontrolled hypertension loses 5.5 work days per year and that 3.5 of the disability days could be avoided if treatment adherence was optimized [142]. It is clear that the potential impact of reduced adherence and persistence on the cost-effectiveness of switching should not be ignored.

Researchers have warned that although formulary access restrictions are designed to reduce costs, '. . . if they cause a drop in patient persistence, or a flurry of activity (switching) with each new list that is adopted, there could be negative consequences for both patients and the Medicaid budget' [110]. This appears to be borne out by recent studies of real-world switching policies that have highlighted the potential 'unintended consequences' of switching and the need to consider more than just drug acquisition costs. A US study of private health insurance found that step-therapy programmes involving ACEIs and ARBs incurred net costs compared with controls (no step-therapy programme) [145]. The step-therapy programme resulted in medication cost savings, supporting the results of an earlier study that looked only at medication costs in a different antihypertensive step-therapy programme [146]. However, antihypertensive use declined and inpatient and emergency room admissions increased in the step-therapy group compared with controls. Gradually the costs incurred increased, such that by 2 years after initiation of step therapy, the average quarterly cost per patient was $99 higher in the step-therapy group than in the control group [145]. Similar findings have been reported in other therapeutic areas. A review of a therapeutic substitution policy for proton pump inhibitors noted that mandated therapeutic substitution may result in higher levels of healthcare resource use. The policy implementation was estimated to have a total net healthcare cost of up to CA$43.5 million [147].

In addition to the economic costs of switching, the human costs should also be considered: what is the impact of switching antihypertensives on patients' quality of life? At present there is little information on this aspect of switching.

To our knowledge, there is no adequately powered, randomized clinical trial demonstrating the cost-effectiveness of a medication switching strategy in hypertension. Any economic model of cost-effectiveness needs to consider a wide range of healthcare resource use and it should also take into account any detriment to patients' quality of life caused by switching.

Conclusions

Although evidence-based medicine should be the primary consideration when selecting optimal patient treatment, medications are an easily identifiable target when healthcare costs are under review. Drug switching with the aim of reducing healthcare costs in hypertension management is

relatively common. However, before implementing a drug switch the potential impact on disease control and the true economic cost must be carefully considered.

The principles of evidence-based medicine should still apply when considering switching drugs. However, a complete and thorough analysis of all the clinical implications of switching has yet to be performed. Medication switching has not been the subject of many clinical trials and much of the data pertain to surrogate markers rather than clinical outcomes. Thus, there is currently little available clinical evidence on which the physician or pharmacist can base his/her decision to switch medications. Differences between medications may be subtle but have long-term consequences that are as yet unknown. For example, antihypertensive agents have different pharmacodynamic and pharmacokinetic properties and potentially different treatment effectiveness, despite belonging to the same drug class. Any switching of antihypertensive therapies can only be implemented after careful consideration of the suitability of a specific drug for a particular individual, taking into account their medical history including comorbidities, concurrent medications and previous therapies. The impact of possible interruptions to optimal drug therapy because of the need for titration should also be borne in mind. The impact of switching must also be considered from the patient's perspective – will switching compromise treatment effectiveness because the patient is dissatisfied with their new treatment? Similarly, the costs incurred through switching need to be carefully analysed. Drug acquisition costs constitute only a small part of the total treatment cost and switching is likely to incur costs through other aspects of healthcare provision, such as additional clinic visits and laboratory tests, as well as costs arising from any adverse effects of switching, including poorly controlled hypertension.

In an ideal world, the question of whether the potential costs of drug substitution in hypertension are outweighed by its benefits would be investigated by randomized controlled trials before such policies are recommended for wide application in clinical practice. However, real-world observational studies and patient databases can also provide useful information on the possible impact of switching medications [148]. Although the cost of treatment should always be considered, such considerations should not predominate over effectiveness and tolerability issues in any individual patient.

Competing interests

Professor Johnston has received reimbursements, fees and funding from pharmaceutical companies including Abbott, Astellas, AstraZeneca, Baxter, Fujisawa, Genzyme, Novartis, Roche, sanofi-aventis, Sterling Winthrop and Wyeth. Professor Johnston owns shares in Abbott, AstraZeneca, Genzyme, Roche, sanofi-aventis and Wyeth. Dr Stafylas has received honoraria and reimbursements from pharmaceutical companies including Boehringer and Novartis. Professor Stergiou has received reimbursements, fees and research funding from pharmaceutical companies including Abbott, AstraZeneca, Boehringer, Bristol-Myers Squibb, Chiezi, GlaxoSmithKline, Lilly, Menarini, Novartis, Pfizer and sanofi-aventis. There is no patent or any intellectual property interests associated with this manuscript.

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