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Generic prescribing – what are the benefits and what are the risks?

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Generic prescribing – what are the benefits and what are the risks?

With the recent Government consultation on generic substitution and the impending patent expiry for the angiotensin II receptor blocker (ARB) class, which began with losartan (March 2010), it is appropriate to review the current debates and policies in development on generic prescribing with particular emphasis on the benefits and risks in different therapy areas.

Depleted public finances augur further productivity improvements

Having experienced significant real growth in NHS funding this century,[1] the present crisis in our public finances is likely to mean that growth in the healthcare budget will be constrained if not eliminated.[1] Over the next spending review period – 2011/12–2013/14 – the budget across all spending departments, including the NHS, could reduce by an average of 2.3% per year[1] and with little or no cash increase from 2011/12 the NHS will need to plan for real terms funding to fall by 2.5–3% per year[2] – equivalent to an £8–10 billion cut over the next Comprehensive Spending Review and up to £15 billion over 5 years.[2] The NHS spends around £9 billion per year on branded prescription medicines in the UK[3] – a figure expected to grow with drug development and an ageing population.[4] One way to increase productivity then, is to reduce NHS drug spending.

Recent Government initiatives to reduce drug costs

The 2009 Pharmaceutical Price Regulation Scheme (PPRS), a voluntary agreement between Government and the Association of the British Pharmaceutical Industry (ABPI), includes measures aimed at reducing NHS expenditure on branded medicines by an average of 5% a year over the 5-year lifetime of the scheme. The measures included a price cut of 3.9% in February 2009 with a further price cut of 1.9% in January 2010 and, subject to discussion with affected parties, the introduction of generic substitution in primary care.[3]

Analysis of the prescriptions dispensed in England from 1998 to 2008 in primary care by The Health and Social Care Information Centre[5] revealed that 83% of prescription items were prescribed generically.[5] This was made up of 65% of prescription items that could be dispensed generically;[5] 18% that, although prescribed generically, were only available as a branded product[3] and 17% that were prescribed and dispensed by the brand name.[3] Although most of this latter 17% were available only as a branded product the Department of Health (DH) noted that 5% were prescribed by brand but were available as a generic, giving a potential increase in the generic prescribing rate to 88%.[3] Closing this 5% gap is the key driver behind the proposed implementation of 'generic substitution',[3] which was open for consultation until 30 March 2010.

'Closing the 5% gap in generic prescribing is the key driver behind the proposed generic substitution.'[3]

Other drivers for cost containment

Commissioners are under tremendous pressure to make savings and this is inevitably likely to mean they must ensure that the cheapest drugs are prescribed wherever possible and unnecessary hospital admissions must be minimised. Implementation of conclusions in health technology appraisals has undoubtedly helped to cap growth in the prescribing budget[6] and some other important tools for cost containment are listed in Table 1.

Anticipated consequences of generic substitution

The main aim of generic substitution is to reduce costs.[7,8] However, at a recent *Chemist and Druggist* (C+D) Senate meeting about proposed generic substitution, the National Clinical Director of Pharmacy,[9] Jonathan Mason, suggested that a longer term benefit might be seen because new drugs can be added to the list of generics available for substitution when they go off patent and

Table 1. Some drivers for NHS cost containment and performance improvement

Quality and outcomes frameworks,[10] practice-based commissioning[4] and guidance from agencies, such as Joint British Societies and NICE[10]	These aim to improve performance by providing an incentive to GPs to meet targets and prevent events from occurring.[10] Also around one-fifth of primary care prescribing is started in hospital and drug choices in general practice are often guided by local specialists. Hospitals limit consultants' prescribing options to drugs approved by the hospital's expert drugs and therapeutics committee as a cost-effective subset of the large range of medicines available.[4] Although not subject to such committees, GPs are urged to review prescriptions originating in secondary care regularly, to see if they are still needed or should be changed.[4]
Better Care, Better Value indicators[4]	Aimed at increasing efficiency in Primary Care Trusts' (PCTs') prescription costs and value for money by highlighting performance variations and where efficiency can be improved.[4] Current indicators are to increase low cost prescribing of proton-pump inhibitors, lipid modifiers and drugs affecting the renin-angiotensin system (specifically the angiotensin-converting enzyme inhibitors [ACEIs]).[4]
Practice-level formularies, prescribing analysis and cost (ePACT) data[11]	These can reflect the cheapest prescribing options and help keep track of spending.[11] They are supported by digital resources such as NHS Clinical Knowledge Summaries (formerly PRODIGY).[11]
Prescribing advisers[10]	They can indicate areas where GPs need to focus on, areas of overspend, or best practice.[11] The National Audit office recommends that all PCTs should support prescribing advisers in seeking to influence GPs' prescribing behaviours in targeted areas by emphasising that value for money includes quality of outcome as well as economy, and that there remains scope for practices to use more expensive drugs when it is clinically appropriate.[4]

this might speed up the shift from branded medicines to generics, which currently takes a long time.

By making a generic substitution a pharmacist could substitute a prescribed branded drug for a generic without consultation with the patient or the doctor who wrote the prescription,[7] unless a doctor ticks a box (or endorses the prescription) to insist on the branded drug[7,8] being dispensed. This would mean that pharmacists could override GPs' prescribing decisions and some pharmacists fear this could lead to friction between prescriber and dispenser.[9] Although some discussants at the C+D Senate meeting were sceptical Mr Mason suggested that when pharmacists need to explain why they are giving a patient something different to what their doctor prescribed, this could present an opportunity to talk to the patient about their medicines.[9] This would have cost and pharmacist time implications that would need to be taken into account and weighed against other priorities, such as improving compliance.[9]

Other discussants at the C+D Senate generic substitution meeting raised concerns about possible legal liability if a substitution led to adverse events (a concern also expressed by dispensing doctors)[7] and about possible penalties if a pharmacist refused to dispense to a patient what they considered to be an inappropriate substitute.[9] The issue of extra workload for pharmacists in managing patient worries about being switched to a generic product was also raised[9] and the DH has identified extra workload for clinicians arising from a need to advise and explain any change to patients as a key issue.[3] The DH is also aware of stakeholders' doubts over whether introducing generic substitution will achieve anything as the system works well now, with a high generic prescribing rate; and the need to exclude certain categories of medicines, such as anti-epileptic drugs (AEDs), for clinical reasons.[3]

Experience with currently available generic drugs

Generic substitution (or formulation substitution) can involve substituting a generic for a branded product, or substituting one generic for another generic product (see Box 1). This necessarily relies upon having demonstrated bioequivalence between all generic substitutes and the branded product. However, alterations in the ionic salt form can cause the generic product to exhibit variability in absorption, pharmacokinetics, drug action and excretion[12] compared with the reference (branded) product. When generic formulations are generated as alternative salts of the branded reference product, they may not always be chemically equivalent and this may translate into differences in therapeutic effectiveness[12] with attendant clinical implications. Such differences are especially important for drugs with narrow therapeutic indices (NTIs), or

Box 1. Generic versus therapeutic substitutions

It is important to distinguish between generic and therapeutic substitutions because they can have different clinical implications.

Generic substitution: The generic product has the same pharmaceutical form and strength as the branded product and its active substance has the same rINN or BAN as the branded product or is a permitted alternative salt of the reference product with an INNM or BANM, which relates to the rINN or BAN for the branded product, unless the rINN covers the salt.[3]

A generic substitute is, therefore, to all intents and purposes, expected to be broadly identical to the branded product (but it should not be assumed that all generics are entirely identical).[12,13]

Therapeutic substitution: This involves substituting the branded product with a generic product from the same therapeutic group or class.[7] It may not necessarily, therefore, have identical clinical indications, mode of action, interactions with co-medication and adverse effects as the reference branded product.

Key: rINN = recommended International Nonproprietary Name; BAN = British Approved Name; INNM = INN Modified; BANM = BAN Modified

with known unpredictable clinical effects or high inter-individual variability.[12] In some cases, a change in salt formulation of a drug can also result in a significant change in molecular weight of the compound, which in turn will necessitate a change in prescribed dose.[12] It is possible that a patient could be dispensed different generic products at presentation of subsequent repeat prescriptions, highlighting the importance of confirming bioequivalence between the various products. Nevertheless, generic prescribing is well-established in general practice with around 83% of all prescription items in England being for generic products[3] and this gives us a wealth of experience upon which to draw when considering the appropriateness of generic substitutions. Although it is not possible to give an exhaustive overview of lessons we can learn from the literature for all generic products, some key points are presented below for some of the major therapeutic drug classes.

Lipid modifiers

Evidence that statins lower total and low-density lipoprotein (LDL) cholesterol and reduce the risk of cardiovascular mortality and morbidity[10] has led to aggressive cholesterol lowering targets[10] and increased the number of patients eligible for treatment.[10] Because NHS spending on statins reached around £600 million per year in 2006[14] a *Better Care, Better Value* indicator for the prescribing of statins was launched[4] in an effort to reduce costs. Simvastatin came off patent in 2003[14] and there was increased pressure and incentive for PCTs to ask GPs to prescribe generic statins.[10,14] There are marked differences in clinical efficacy between 'older' statins, such as simvastatin and pravastatin, and newer ones, such as atorvastatin and rosuvastatin, but the argument for a 'class effect' once efficacy differences are taken into account is fairly convincing.[14] Nevertheless, in a paper on this subject Goldsmith cautioned that 'we must always act in the patient's best interest, catering for the individual rather than the population as a whole'.[14] In a back-to-back paper Duerden quoted a small, carefully-conducted audit from a primary care practice in Herefordshire[15,16] in which patients were individually assessed to see if a switch from atorvastatin to simvastatin was appropriate.[14] A 2-year follow-up report showed that of the 69 patients who switched, 61 of the 65 who were still registered at the practice were still taking simvastatin – and 58 of these were still taking the same dose. There was no significant change in mean total cholesterol over the 2-year period.[14] Duerden concluded that 'in the case of statins switching to cheaper alternatives such as simvastatin can be done safely with no loss of clinical benefit'.[14]

'We must always act in the patient's best interest, catering for the individual rather than the population as a whole.'[14]

A Bandolier review of switching statins concluded that atorvastatin 10mg and simvastatin 40mg are virtually identical in terms of their average effect in lowering total cholesterol and LDL cholesterol, although there was little in the way of a significant dose-response.[17] Two studies of switching statins – one from a large US institute and the other from the Herefordshire practice[15,16] – showed that switching statin was feasible and cost-effective.[17] However, Bandolier emphasised an important caveat to 'top-down' rulings on prescribing policy, citing a case example in which an evidence-based policy to give atorvastatin 40mg or 80mg to patients after myocardial infarction (MI) or revascularisation was overruled by local PCTs (the funders of healthcare) and the local NHS Trust (the provider of secondary and tertiary healthcare) limiting prescribing of atorvastatin[17] and instituting a switch to generic simvastatin 20–40mg.[17,18] An audit over the same calendar period under the successive policies (high-dose atorvastatin and low-dose simvastatin) showed the simvastatin policy resulted in more deaths (17% of the low-dose simvastatin group versus 5% in the high-dose atorvastatin group)[18] and cardiac and non-cardiac readmissions.[17] Bandolier suggested that this raises important questions about who is responsible for the consequences of such prescribing decisions.[17] The audit researchers felt that 'wholesale change from an effective treatment to one less efficacious might adversely affect patients' morbidity and mortality' and that 'the cost of the additional cardiac readmissions will almost certainly offset the additional cost of the high-dose statin therapy'.[18]

Bandolier highlighted the need for long-term outcome data on statin switches concluding that 'the payer may be saving on one budget and spending on the other'.[17] These issues were in broad agreement with the following key points that were made by a panel of experts convened by the *British Journal of Cardiology* to debate the issues and implications of switching statins.[10]

1. The cost consideration of a statin needs to be balanced with its clinical effectiveness, the impact on health economics, mortality, morbidity and quality of life, as well as the wider implications on care costs such as the increased risk of hospitalisation. This includes (considering): i) compliance – if reduced this might increase the risk of an event; ii) the dose titration of a new drug which requires more GP visits; iii) intolerance or side-effects to a new drug which can increase risks and iv) adverse events.

'The cost consideration of a statin needs to be balanced with its clinical effectiveness, the impact on health economics, mortality, morbidity and quality of life, as well as the wider implications on care costs such as the increased risk of hospitalisation.'[10]

2. If a switch is to be undertaken it needs to be done responsibly and systematically ensuring the following aspects are incorporated: i) a review of the suitability of patients (on a careful review as many as 50% may be ruled out); ii) consultation with the patient to ensure compliance is not jeopardised; iii) follow-up and review of patients at 3 months to monitor progress, side-effects, and the need for up or down titration.

The panel concluded that 'increased pressure for GPs to switch patients from branded to non-branded medications may superficially look attractive, but it is clear that there are many considerations and implications involved that need to be carefully thought through'. Considerations they felt were important included: attainment of new lower cholesterol targets; practice-based commissioning and the significant impact of keeping patients out of hospital; balancing the cost of a statin with its clinical effectiveness.[10]

'Wholesale change from an effective treatment to one less efficacious might adversely affect patients' morbidity and mortality.'[18]

Other cardiovascular drugs

In a systematic literature review of publications during 1984–2008, 47 articles were identified that allowed clinical differences arising from use of generic and brand-name drugs – primarily for treating cardiovascular disease – to be compared.[19] The cardiovascular drugs were classified as having a narrow or wide therapeutic index (WTI)[19] and measured clinical outcomes included vital signs; clinical laboratory values such as INR (international normalised ratio) and urine electrolytes; adverse effects or other morbidity; and healthcare system utilisation including clinic and emergency department visits.[19] The best evidence for clinical equivalence in WTI drugs emerged from high-quality prospective randomised controlled trials in patients with cardiovascular disease involving β-blockers, calcium channel blockers (CCBs) and statins. The studies concluded that generic and brand-name cardiovascular drugs were similar in nearly all clinical outcomes. Fewer trials compared generic and brand-name diuretics, anti-platelet agents, ACEIs and α-blockers, thus limiting the authors' ability to reach conclusions.[19] Warfarin was the most studied NTI drug; six prospective studies found similar clinical outcomes with branded and generic warfarin, including INR, required dose adjustments and adverse events, but two retrospective reviews revealed transient differences in INR after changes from brand-name to generic warfarin without any differences in clinical outcomes. The authors felt that taken as a whole, these findings suggest that switching from brand-name to bioequivalent generic warfarin products is safe, although it may be useful to monitor the INR of higher-risk patients more closely during a switch period.[19]

Limitations of the analysis were that most of the bioequivalence studies were powered to assess differences in pharmacokinetic parameters rather than clinical outcomes, and most clinical outcomes were tested by a superiority rather than non-inferiority hypothesis, which means that it is not valid to conclude that agents are equivalent, only that there is insufficient evidence to conclude they are different. Also, many studies included disproportionately young and healthy subjects, and there were limited comparisons in patients with multiple morbidities and taking numerous medications. Such patients may be at greater risk of adverse events if modest clinical differences in medication formulations exist. Finally, most studies were short-term evaluations and did not collect the data necessary to compare long-term outcomes associated with generic drug use such as rates of MI or death. Bearing these limitations in mind, the authors concluded that 'it is reasonable for physicians and patients to rely on a FDA bioequivalence rating as a proxy for clinical equivalence among a number of important cardiovascular drugs, even in the higher-risk NTI drug warfarin'.[19]

The need to assess every potential generic switch is highlighted by research data suggesting that demonstration of chemical equivalence and bioequivalence for anti-arrhythmic drugs (AADs) does not guarantee therapeutic equivalence.[20] The researchers surveyed clinical electrophysiologists about their experience with generic AADs[20] and found recurrences of tachyarrhythmia and cases of proarrhythmic events in association with AAD formulation substitutions, some of which were fatal.[20] Several cases were documented by associated changes in serum drug concentrations after switching to generics or from rechallenge studies.[20] Possible explanations for therapeutic inadequacies seen in this study were also thought to relate to bioequivalence tests being generally conducted in normal, healthy adults with a lack of consideration of the effect of drug interactions.[20] In addition, older patients with arrhythmias may have concurrent diseases, such as heart failure, and may frequently be taking other medications – with consequent age-related alterations in pharmacokinetics.

Psychoactive drugs

Unreliable compliance and suspicion of change are common in people with schizophrenia.[21] Therefore, although generic substitution in this group could save drug costs, when compliance is negatively affected this can be outweighed by poorer symptom control and increased hospitalisation costs.[21] A recent study quantified the health economic impact of generic substitution by comparing patients (using a discrete event simulation model) who were either maintained on branded risperidone or switched to generic risperidone.[21] The model used assumed generic risperidone cost 40% less than the branded product and tested the effect of reductions in compliance of between 2.5% and 10% after generic substitution on treatment costs. The authors found that it would be more cost-effective (using NICE threshold of £30,000 per quality-adjusted life year gained) to maintain patients on branded risperidone when the probability of non-compliance exceeded 5.2% with generic substitution.[21] Since the study authors note that non-compliance rates for patients suffering from schizophrenia reported in the literature are relatively high, ranging from 40–50%[21] it would seem unlikely that generic substitution would be a cost-effective strategy in this patient group. However, this area clearly needs proper evaluation before conclusions can be drawn.

A review of the literature between 1975–2003 found that few publications compared the bioequivalence and efficacy of brand-name and generic psychoactive drugs.[22]

However, in those that were identified, differences in the efficacy and tolerability of brand-name and generic psychoactive drugs that had not been noted in the original bioequivalence studies, were found.[22] This included statistically significant differences in pharmacokinetic variables in favour of brand-name versus generic diazepam and a case report involving paroxetine mesylate, which cast doubt on the tolerability and efficacy of the generic formulation, leading the investigator to conclude that the 'essential-similarity requirement' (between a generic product and its reference branded product) should be extended to include more rigorous analyses of tolerability and efficacy in actual patients as well as in healthy subjects.[22]

Anticonvulsants

Epilepsy is a condition in which consistency of treatment is paramount to successful management and even a single breakthrough seizure could put the patient at immediate risk for injury, loss of income, driving privileges or death.[23] Many newer generation AEDs have now come off patent and there are anecdotes – small retrospective analyses and surveys[23] that have reported breakthrough seizures after treatment change, which have raised concerns about the interchangeability of generic and branded AEDs. Liow (2009) pointed to two recently published studies[24,25] in which medical/pharmacy claims data were evaluated for rates of switch back among users of AEDs compared with other therapeutic areas.[23] In both studies, a higher propensity to switch back from generic to branded medications was observed for AEDs than for non-AEDs and in both studies a statistically significant difference in AED dose was found for those patients not switching back.[23–25] One of the studies highlighted the fact that switching patients to generic lamotrigine from the branded product was significantly associated with increased physician visits and hospitalisations,[24] which is in accord with a Danish study in which seizure relapses occurred in some patients after switching their lamotrigine preparation, accompanied by significant changes in lamotrigine plasma concentrations.[23]

Another literature review found a report of several controlled studies in which seizure recurrence was seen after switching from branded to generic carbamazepine; a sudden recurrence of seizures when generic valproic acid was substituted for the brand-name product (the US FDA found a difference in bioavailability between the two formulations), and a 31% reduction in plasma phenytoin concentrations after switching from a branded to generic product.[22] As Privitera points out: 'subtle differences in pharmacokinetic parameters between two formulations could produce clinically important differences in adverse effects or seizure control'. Extra caution may be needed for patients at highest risk of seizure complications, such as pregnant patients, patients with recurrent status epilepticus or patients who have been seizure-free for long periods of time and are driving.[26] In recognition of such concerns, regulatory bodies in several European countries have issued guidance or policies relating to non-substitution of certain AEDs, thus acknowledging epilepsy as a critical disease.[27]

Impending patent expiries – angiotensin II receptor blockers

In hypertensive patients aged 55 years or more, or black patients of any age, national guidelines recommend that initial therapy should be either a CCB or thiazide-type diuretic.[28] If younger than 55 years, initial therapy should be an ACEI. Where a second or third drug is needed, an ACEI can be added to a CCB or thiazide-type diuretic or vice versa, or to both[28] as necessary. ARBs are currently only recommended when ACEIs are not tolerated – estimated to be up to 20% of cases.[28] The patent expiry of losartan in the ARB market might act as a stimulus, along with significant financial pressures, to switch patients to the generic agent with the lowest acquisition cost. Although cost savings could be made per prescription item using this strategy consideration must be given to the factors that will impact upon cost savings, as shown by Usher-Smith and colleagues (see Box 2).[15,16] This includes the time spent by the pharmacist and GP screening patients, postage for the notification of switch letter and additional appointments before the switch, which reduces the first year savings. Further savings will depend upon the market conditions, and future savings projections could be serious over estimations, as found by Usher-Smith.[16]

To address this difficulty in projecting savings in a falling market, Belsey (2008) modelled the 5-year cost-consequences of a switch strategy based around an assumption of equal blood pressure lowering efficacy across the ARB class in a typical population with mild-to-moderate hypertension.[6] The

Box 2. Case study of switching patients from branded losartan to branded candesartan[15,16]

A recent study was undertaken in a UK primary care practice where the local PCT had requested suitable patients to be switched from losartan to candesartan for the purposes of cost saving.[15,16] The researchers identified 137 patients as currently being prescribed losartan. Of these, 121 were considered suitable for switching and 108 were successfully changed (six refused to change and seven switched back). Net savings of £13,374[16] were made in the first year after deducting the one-off costs of making the switch.[16] The authors concluded that significant savings would only continue to be achieved until the patent expiry of the branded losartan and 'this raises issues about the ethics of continually chasing cost savings as the prices of drugs change'.

In a subsequent review of this study[16] they emphasised that there was a significant financial cost to the practice of performing the switch and the number of patients excluded highlights the importance of carefully reviewing patients and not switching patients inappropriately.[16] An important update was appended to this article by the authors, which underlines the unpredictability of future financial projections. They stated that 'the price of losartan was decreased so that at (the then) current pricing the annual saving for the practice was reduced from £14,008 to £5,324'. They added that this 'highlights the fact that any switch performed for cost-saving purposes is dependent upon the market and so the saving is unpredictable'.[16]

Table 2. ARB licensed indications in addition to essential hypertension and patent expiry dates

Angiotensin II receptor blocker	Expected patent expiry	Adult licensed indications in addition to essential hypertension
Losartan (Cozaar)	Expired March 2010	Treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus with proteinuria 0.5 g/day as part of an anti-hypertensive treatment. Treatment of chronic heart failure in patients >60 years old, when treatment with ACEIs is not considered suitable. Reduction in the risk of stroke in adult hypertensive patients with left ventricular hypertrophy documented by ECG.[29]
Valsartan (Diovan)	May 2011[6]	Treatment of clinically stable patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours–10 days) MI. Treatment of symptomatic heart failure when ACEIs cannot be used, or as add-on therapy to ACEIs when ß-blockers cannot be used.[30]
Candesartan (Amias)	April 2012[6]	Treatment of patients with heart failure and impaired left ventricular systolic function (left ventricular ejection fraction 40%) as add-on therapy to ACEIs or when ACEIs are not tolerated.[31]
Irbesartan (Aprovel)	August 2012[32]	Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an anti-hypertensive regimen.[33]
Telmisartan (Micardis)	January 2014[34]	Reduction of cardiovascular morbidity in patients with atherothrombotic cardiovascular disease (history of coronary heart disease, stroke or peripheral arterial disease) or type 2 diabetes mellitus with documented target organ damage.[35]

aim was to determine the switch option that offered the best value for money in a context of changing price structures. Only prescribing costs were considered in the Markov model, and all ARB agents were assumed to produce the same reductions in diastolic blood pressure at their starting doses and at the higher doses they would be titrated to, with no assumptions being made regarding the likely impact on clinically significant cardiovascular outcomes, although the author acknowledged that a class-effect remains unproven for the ARBs.[6] The model was based upon the cost-decay curve of ramipril, which after 8 months had reached 22% of its pre-expiry price and then levelled off. The author felt this would be more comparable with the potential situation of the ARBs than would simvastatin, which reached 25% of its branded price after 15 months, probably reflecting the extreme competitiveness of the large statin market.[6] At the time of the study candesartan was the lowest-priced ARB, followed by losartan and irbesartan, followed by valsartan. All prices were estimated to deflate to 22% of their baseline values over a 7-month period after their expiry. Based upon the different dates of patent expiry (see Table 2), the author estimated that a losartan-based regimen represented the least costly option under the conditions of the model.

This analysis serves to illustrate the complexities in making projections. The author recognised that the cost-decay curve following patent expiry differs from one drug to another and is difficult to predict because it depends upon market-driven issues,[6] reflecting the clinical experience of Usher-Smith and colleagues.[16] He concluded that switching hypertensive patients taking ARBs to the agent with the lowest current acquisition cost may yield only transient budgetary savings.[6] An equally important consideration noted by Belsey is that not all ARBs share the same licensed indications (see Table 2). Within the UK, for instance, some ARBs (eprosartan[36] and olmesartan[37]) are purely licensed for uncomplicated hypertension, others are licensed for use in patients where there is left ventricular dysfunction or enlargement (losartan, candesartan and valsartan), in patients with diabetic nephropathy (losartan and irbesartan) or following MI (valsartan),[6] and for both early- and late-stage renal disease in hypertensive type 2 diabetic patients as part of an anti-hypertensive regimen (irbesartan).[33] Belsey also highlighted common concerns about ensuring that legal responsibility is assigned and clear when generic or therapeutic substitutions are made to patients' medication.[6]

Conclusions

It is widely acknowledged that NHS savings are necessary and significant savings are already being achieved, but the worry is that as commissioners' budgets become squeezed even further, pressures to make therapeutic

switches (from branded to generic products of the same drug class) in addition to generic switches (to pharmacologically and bioequivalent products) will increase, perhaps to the detriment of the patient. There is, therefore, an urgent need for the bearer of responsibility for prescribing decisions (for example, the PCT or GP) and for generic substitutions (for example, the dispenser or pharmacist) to consider the real value of generic prescribing.

Some general conclusions drawn from the literature in terms of some of the perceived benefits and limitations of generic prescribing or generic substitution are given in Box 3. Although these examples are not exhaustive they reflect general themes within the literature.

In summary, lessons learned from the literature include the need, before switching

a patient from a branded to a generic medication, to consider:

- current patient response to existing treatment (if well-controlled, the patient should not be switched) and those with certain medical conditions (such as epilepsy[23]) or particular sensitivities should not deviate from their regular medication.[7] The importance of exercising particular caution with NTI drugs and highly variable drugs has been emphasised[23,38,39]
- the appropriateness of the intended medication for the patient's specific medical condition (ie whether the medicine is licensed for the specific indication)
- patient-specific co-morbidities and co-medications. These should be reviewed to ascertain whether they could be modified adversely by the intended switch[38]
- patient views about switching, including their previous experiences and preconceptions.[21,23] Concordance is well-known to influence compliance and, ultimately, patient outcomes, and it is therefore important to maximise this
- the need for pre- and post-switching monitoring of clinical status, clinical biochemistry, therapeutic drug monitoring and compliance checking should be assessed.[15] The associated cost-implications of any switch (generic or therapeutic) should also be factored in alongside whether the potential disruption to the patient is justified by the magnitude of likely returns[6]
- whether it is cost-effective to switch from a branded to a generic drug if the brand has only a very short interval before patent expiry. Based upon experiences reported in the literature,[15] first year savings are reduced by administrative and clinical costs, and further savings erosion will occur as branded drugs costs fall.[16] From this experience it seems unlikely that significant cost-benefits can be achieved during very short intervals between expiry dates of the ARBs, particularly in a market of falling brand prices.

The next article in this mini-series will focus on the perceptions of generic medicines by patients and by healthcare professionals, and the potential cost-benefits of generic switches.

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Box 3. Benefits and limitations of prescribing generically and generic substitution

Benefits of prescribing generically

Cost savings may be made (separate draft assessing the cost impact has been compiled by the DH).[3]

Dispensers are provided with greater flexibility on the products they dispense to patients, so patients may obtain their medicines more quickly and less stock has to be held by the pharmacy (which in turn leads to savings for the NHS).[3]

Limitations of prescribing generically

Bioavailability differences between generic and branded products seen in patients can lead to overdosing or underdosing.[23] Multi-dose bioavailability studies, that are the more representative of 'real life' situations, should be conducted in patient populations rather than single-dose studies conducted in healthy, young adults, as is the usual setting for such studies.[23,40]

Switching drugs in primary care requires very careful patient selection – when switching patients from atorvastatin to simvastatin, up to 50% of patients were considered unsuitable in a recent study.[16]

Switching from a branded to a generic class-similar drug might not be appropriate if the products do not have identical indications.[6] For example, only two ARBs have an additional license indication for treatment of renal disease in patients with diabetes and hypertension: irbesartan[33] and losartan.[29] Trials with irbesartan demonstrated renal protection in both early and late stages of renal disease,[41,42] and losartan demonstrated protection in late-stage renal disease[43] (protection in early-stage renal disease has not been investigated).

Bioequivalence, as defined by European and American regulatory authorities, implies but does not guarantee therapeutic equivalence.[40]

Therapeutic switches are time consuming, incur financial costs and may cause significant irritation to patients.[6]

There is potential for the patient to experience confusion arising from a switch,[7,9] particularly those who take several medicines and the elderly.

There is potential for substitution errors to be made[7] and for duplication of medicines with similar effects.

There are concerns about reduced compliance following medication switches.[7,9] Good communication with patients is important[16] in this regard.

Perceived correction of a doctor's prescription may cause the patient to question the doctor's competence, and could adversely affect the relationship between a patient and the GP or medical services.[7]

When making an assessment of future financial savings it must be remembered that the cost of drugs is not fixed, and companies may subsequently change the price, reducing the degree of savings.[16]

If an error occurs or harm befalls a patient following generic substitution, it will be essential to determine who is responsible.[7,9] This is currently unclear.

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Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk.

Adverse events should also be reported to Bristol-Myers Squibb Pharmaceuticals Ltd Medical Information on 0800 731 1736, medical.information@bms.com

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