Drug reimbursement: Indicators of inappropriate resource allocation

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Aims In many countries, governments and third parties find themselves paying for (reimbursing) unproven, inadequate products limiting their ability to invest in therapies with evidence of relevant patient benefit. We examined how three characteristics, level of therapeutic evidence, susceptibility of inappropriate prescribing, and intercountry variation can be used to identify inefficiencies in pharmaceutical reimbursement among four European Union countries, Austria, Belgium, the Netherlands and Sweden.

Methods Specific classes of medicines were chosen to provide useful examples of how healthcare resources could be reallocated. A high level of therapeutic evidence was defined as a substantial body of evidence in at least one indication with clear-cut support of relevant patient benefit. The susceptibility of inappropriate prescribing was defined as the likelihood of prescribing a drug outside the scenario for which clear-cut evidence (if any) has been documented to produce relevant benefit for the patient. The intercountry variation represents the variation in utilization of reimbursed drugs across the four countries.

Results The combination of these characteristics provides a useful tool for assessing appropriate reimbursement decisions. It would be beneficial to healthcare payers as well as patients to move resources from products that have a low level of therapeutic evidence and a high susceptibility of inappropriate prescribing to products with a high level of therapeutic evidence and low susceptibility of inappropriate prescribing, and to use intercountry variation as a signal of drug classes that should be subject to further scrutiny.

Conclusions A method is presented to help policy-makers identify inefficiencies in the spending of limited health care resources, and to reallocate resources to products that have been shown to improve patient care through evidence-based medicine.

Keywords: drug utilization, evidence-based medicine, pharmacoeconomics, reimbursement policy

Introduction

Most European countries have at least four to five thousand drugs available on the market [1, 2]. Despite this apparent plethora, it would be hard to argue that we are not in need of new medicines, e.g. with an improved benefit-risk profile.

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However, the cost of medicine is becoming an increasingly contentious issue and health care payers are grappling with ways to manage rising costs with limited resources, while patients continue to demand equal access to increasingly high quality medical care. Reference pricing, formulary restrictions, and budgetary control are just a few of the many strategies that have been implemented by various payers to contain the expenditures spent on medicines [3–5, 6]. However, in the past, the success and public acceptance of such measures have been mixed [6, 7]. We here propose and subsequently illustrate with specific examples a new perspective on how to improve resource allocation as it pertains to medications. Our

analysis focuses on the level of therapeutic evidence, susceptibility of inappropriate prescribing and intercountry variation of drug utilization.

We illustrate the relationship among these attributes by comparing utilization of 19 drug classes in four of the smaller European Union member states (Austria, Belgium, the Netherlands and Sweden) that are comparable in respect of standards of living and health care, availability of resources, and epidemiology.

Methods

Selection of drug classes

Specific classes of medicines were chosen to provide useful examples of how health care resources could be reallocated based on inspection of the drug utilization data, and/or *a priori* awareness of insufficient evidence, and/or *a priori* awareness of increased susceptibility of inappropriate prescribing. When clear epidemiological evidence of population characteristics, that could effect drug utilization, varied between countries, drug classes in that therapeutic area were excluded (e.g. anti-infectives). Several drug classes were also excluded from analysis due to complexities that could not be fully addressed in this analysis. For example, benign prostatic hypertrophy is often treated with herbal remedies, and the available utilization data do not necessarily include accurate information on herbal products [8].

Level of therapeutic evidence

The level of therapeutic evidence for each drug class was dichotomized into 'low' and 'high'. Only those classes of drugs were classified as 'high' for which there was a substantial body of published evidence of relevant patient benefit. Thus, all classes of drugs for which there was no therapeutic evidence or only trials showing improvement of a surrogate as opposed to clinical outcome were classified as 'low' (e.g. antiglaucoma preparations).

Information used to determine the level of therapeutic evidence for each therapeutic class of drugs was obtained primarily from the data produced by the Cochrane Collaboration [9]. The Cochrane Collaboration is a non-profit international organization that prepares systematic reviews of the healthcare intervention literature. If relevant information was not available in the Cochrane Library, a review of the medical literature identified through MEDLINE was employed.

Susceptibility of inappropriate prescribing

Like the level of therapeutic evidence, the susceptibility of inappropriate prescribing was dichotomized into 'low' and 'high'. The susceptibility of inappropriate prescribing was defined as the proven likelihood based on literature reports of prescribing a drug outside the scenario for which clear-cut evidence (if any) has been documented to produce relevant benefit for the patient. It should be noted that this is not necessarily the same as approved indication.

The susceptibility of inappropriate prescribing for each of these classes of medications was determined by identifying strong signals in the medical literature indicating a consistent pattern of inappropriate prescribing. Together these attributes are displayed in Figure 1 with four quadrants (low susceptibility of inappropriate prescribing, low level of therapeutic evidence [I]; low susceptibility of inappropriate prescribing, high level of therapeutic evidence [II]; high susceptibility of inappropriate prescribing, low level of therapeutic evidence [III]; high susceptibility of inappropriate prescribing, high level of therapeutic evidence [IV]).

Inter-country variation

We performed a simple descriptive analysis of the drug utilization data by reimbursement level for each country. Ideally, defined daily dose (DDD) data should be used when making comparisons across countries [10, 11]. However, this data could not be obtained for each of the four countries therefore the analyses were based on outpatient prescription units dispensed provided by Intercontinental Medical Statistics (IMS) for Austria, Belgium, and the Netherlands and Läkemedelsstatistik AB (LSAB) for Sweden [12, 13].

Despite the complex reimbursement schemes in each country, reimbursement status, for the purposes of this report, was crudely dichotomized into reimbursed (any reimbursement level) and not reimbursed. Only reimbursed medicines were included in the analyses in order to focus on the third party payer perspective.

Inter-country variation represents the variation in drug utilization across the four countries. Weighted utilization per drug class was calculated as a product of the percent of all reimbursed units sold that were for that drug class with a country-specific weight. The country-specific weight was calculated as the total number of prescriptions in 1998 divided by the total population in 1998 in a given country. This weight was used to eliminate any differences between countries in terms of the absolute number of prescriptions consumed *per capita*.

Weighted utilization per drug class = [(units sold in a drug class)/(total reimbursed units sold of all drugs) × 100%] × [(total number of prescriptions per year)/(population)]

Variability of utilization per drug class across the four countries was expressed in the form of a coefficient of variation, calculated as a ratio of standard deviation of

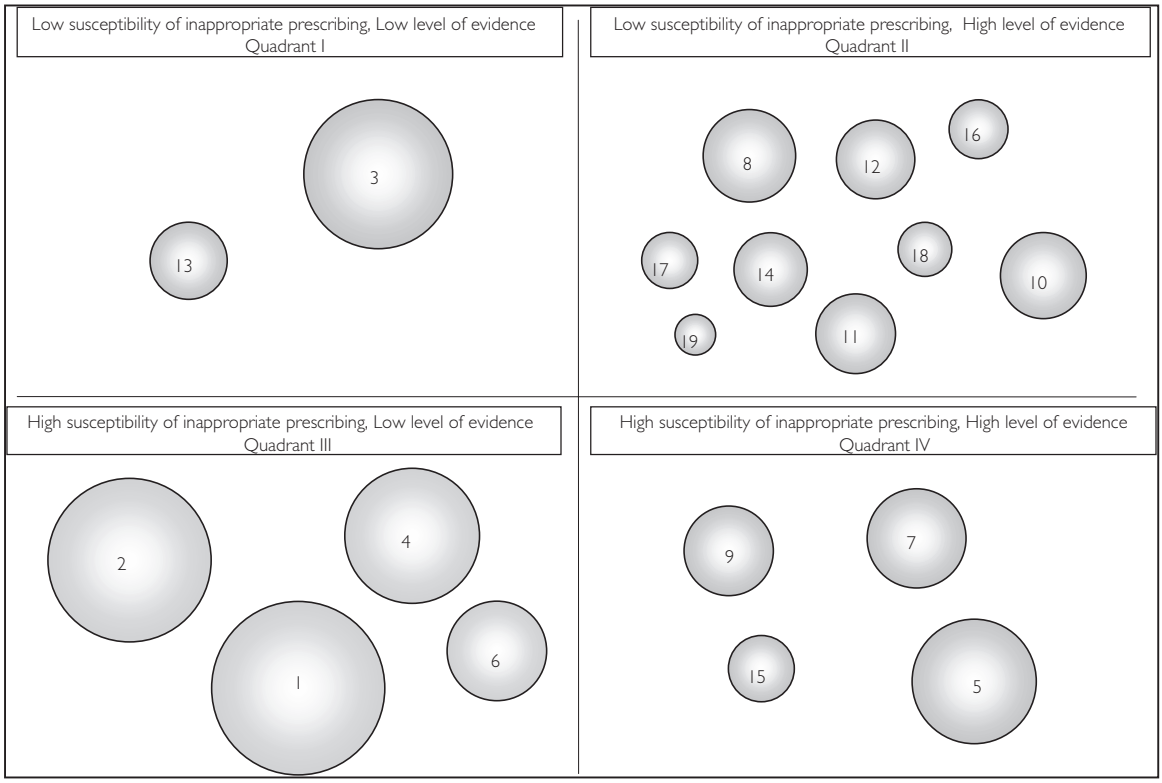

Figure 1 Susceptibility of inappropriate prescribing, level of therapeutic evidence, and intercountry variation for Austria, Belgium, the Netherlands, and Sweden (1998).

	Drug classes	*Examples*	*Coefficient of variation*
1	C04A	Peripheral vasodilators (cinnarizine, nimodipine, etc.)	196.99
2	N06D	Anti-dementia drugs (piracetam, levocarnitine, etc.)	179.56
3	C10A B	Fibrates (gemfibrozil, clofibrate, etc.)	156.26
4	H05B A	Calcitonin preparations	135.71
5	N05C	Hypnotics and sedatives (temazepam, phenobarbitone, etc.)	121.21
6	R05C	Expectorants (acetylcysteine, guaifenesin, etc.)	92.05
7	H01A C	Growth hormone (somatropin)	91.41
8	R03D A	Xanthines (theophylline, aminophylline, etc.)	85.01
9	A02B C	Proton pump inhibitors (omeprazole, lansoprazole, etc.)	82.10
10	R03B A	Glucocorticoids, inhalants (beclomethasone, budesonide, etc.)	78.80
11	C10A A	HMG CoA reductase inhibitors (simvastatin, pravastatin, etc.)	73.53
12	N03A	Antiepileptics (phenytoin, carbamazepine, etc.)	72.55
13	S01E	Antiglaucoma preparations and miotics (pilocarpine, timolol, etc.)	71.24
14	M05B	Drugs affecting mineralization (alendronate, etidronate, etc.)	68.59
15	R03A	Adrenergics, inhalants (salbutamol, salmeterol, etc.)	63.16
16	N04	Anti-Parkinson drugs (levodopa, bromocriptine, etc.)	58.21
17	A07E	Intestinal anti-inflammatory agents (sulfasalazine, mesalazine, etc.)	56.43
18	A10A	Insulins and analogues	55.40
19	H03B	Antithyroid preparations (thiamazole, propylthiouracil, etc.)	48.83

weighted utilization per drug class with the mean of weighted utilization per drug class multiplied by 100%.

Coefficient of variation per drug class = [(standard deviation of weighted utilization per drug class)/(mean of weighted utilization per drug class] × 100%.

Coefficient of variation was plotted as bubbles on Figure 1 and the radius of each bubble is proportional to the measure of intercountry variation. The placement of each bubble in the respective quadrants and the relative location compared to the other bubbles is arbitrary

because of the lack of evidence to allow specific positioning.

We also calculated the proportion of total units and the proportion of expenditure they represent in each of the four quadrants as well as the proportion of total expenditure by these 19 classes of drugs relative to all reimbursed expenditure in a given country.

Results

Nineteen classes of drugs were chosen for this analysis, two of which fall in quadrant I, nine in quadrant II, four in quadrant III, and four in quadrant IV (Figure 1). The therapeutic drug classes with their World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) code that were chosen for analysis are listed in the legend to Figure 1 [8]. The utilization of products from these 19 classes of drugs represent 15%, 17%, 19%, and 17% of all available reimbursed units dispensed for Austria, Belgium, the Netherlands and Sweden, respectively. In terms of expenditure, the 19 classes represent 21%, 24%, 36% and 27% of the total expenditure for all reimbursed drugs in Austria, Belgium, the Netherlands and Sweden, respectively, in 1998. We have also noticed that the consumption of reimbursed drugs per inhabitant does not vary extensively between these countries (range from £0.06 to £0.10 per inhabitant[1].

The following six classes of drugs were placed in the low evidence category (quadrants I and IV) because of failure to show sufficient efficacy on the relevant endpoints: no decrease in mortality [14, 15] (fibrates); no decrease in the loss of visual acuity [16] (miotics and antiglaucoma drugs); no long-term improvement in cognitive function [9, 17, 18] (cerebral/peripheral vasotherapy and nootropics); no clinically relevant improvement in respiratory performance [19] (expectorants), and no impact on risk of fracture (calcitonins) [20, 21].

The following reasons were used to justify the placement of these nine classes of drugs in the high susceptibility of inappropriate prescribing group (quadrants III and IV): prescribed extensively beyond indication without adequate evidence [22, 23] (proton pump inhibitors, calcitonins); symptomatic relief only, which may result in poor disease management [24, 25] (β_2-adrenoceptor agonists); social pressure [26] (growth hormone); medicalization of social problems [27, 286] (cerebral/peripheral vasotherapy, hypnotics/sedatives, antidementia drugs); and abuse (expectorants) [29].

From Figure 1 it can be seen that generally, the classes of drugs that fall in quadrant II (low susceptibility of inappropriate prescribing, high level of therapeutic evidence) have the lowest intercountry variation, and the classes in quadrant III have the greatest intercountry variation. The two drug classes with the greatest intercountry variation were peripheral vasodilators (quadrant III) and antidementia drugs (quadrant III) and the two with the lowest intercountry variation were insulin (quadrant II) and antithyroid drugs (quadrant II). The proportion of total units[2] among the 19 classes studied in each of the four quadrants is as follows: 15% of units fall in quadrant I, 44% in quadrant II, 16% in quadrant III and 26% in quadrant IV. Within the 19 classes, the highest proportion of expenditure on reimbursed drugs was spent in quadrant II (mean 55.2%, range 47.8–60.7%) and the lowest in quadrants I (mean 4.8%, range 2.15–9.7%) and III (mean 4.85%, 1.94–21.99%). Quadrant IV accounted for 35.1% of the total expenditure for reimbursed drugs among the classes studied.

Discussion

Figure 1 is a useful tool for learning about the interplay of the level of therapeutic evidence of available therapeutics and the susceptibility of inappropriate prescribing leading to a certain level of intercountry variation. Clearly, the most ideal location is quadrant II, meaning there is low susceptibility of inappropriate prescribing and a high level of therapeutic evidence. Drugs that fall in this quadrant are obvious candidates for reimbursement because they are likely to be used correctly and provide relevant patient benefit.

The appropriate way to increase the level of therapeutic evidence is to conduct scientifically rigorous and independent studies. However, it should be noted that data from additional studies will not address the problems associated with a high susceptibility of inappropriate prescribing. This is illustrated by the example of proton pump inhibitors, for which there is indisputable evidence of their efficacy in many indications. However, they are used for a variety of reasons such as minor complaints of dyspepsia which could easily be treated with cheaper products [22].

Quadrant IV contains those products that have a high level of therapeutic evidence, but also a high susceptibility of inappropriate prescribing. In order to avoid waste among these classes of drugs, the focus of health care authorities should be on the implementation of good health care practices including development and adherence to treatment protocols and educating physicians and patients. As an example, improving education about the appropriate use and the risk of over prescribing β_2-adrenoceptor stimulants for asthmatics with targeting

[1]Purchase Power Parity adjusted exchange rate was used for 1998. (OECD data)

[2]Weighted units within the 19 classes of reimbursed drugs

pharmacotherapy to the underlying inflammation process could produce tremendous improvements in patient care [24]. It is important to realize that being in this quadrant should not prevent making these drugs available to those who could truly benefit from them. The message here is that inappropriate resource allocation is mainly due to nondrug effects, e.g. irrational use, lack of information, outdated standards or treatment and the like.

Quadrant III contains those products that have a low level of therapeutic evidence and a high susceptibility of inappropriate prescribing, and should be the primary target for resources that can be reallocated to products that can improve patient care and can potentially reduce inefficiencies in the delivery of health care. Examples of recent health care policy decisions to remove ineffective drugs from reimbursement lists are becoming more common, but they are still too far and few between. For instance, France decided to no longer reimburse vitamins and 'antifatigue' drugs in 1987 and 1993, respectively. In 1993, the Netherlands removed homeopathic medicines from their reimbursement scheme and more recently, Germany removed expectorants from the list of reimbursed products (1999).

Quadrant II, as mentioned above, contains the drug classes that are most suited for reimbursement because they have a high level of therapeutic evidence and low susceptibility of inappropriate prescribing, however, this does not mean that drugs in this quadrant should not receive attention from health authorities. It is important that these drugs remain in quadrant II without floating to quadrant IV by preventing an increase in their susceptibility for inappropriate prescribing. Ideally, this can be accomplished with the implementation of good health care practices as described above.

Quadrant I contains those classes of drugs that have been categorized with a low level of therapeutic evidence but a low susceptibility of inappropriate prescribing. It can be argued that the first priority of a health authority as it pertains to making drug policy decisions would be to remove those drugs that have little evidence of providing patient benefit, regardless of their susceptibility for inappropriate prescribing. However, this line of thought cannot be systematically applied to quadrant I as it was proposed for quadrant III, making it difficult to offer a recommended action for drug classes appearing in this quadrant. As illustrated by the case of antiglaucoma drugs, a number of drugs are still reimbursed on the basis of showing improvements in surrogate endpoints only (in this case, intraocular pressure). More studies with clinical endpoints are required on these classes of drugs before a decision can be made that could potentially harm patients.

Since the early days of the WHO, intercountry variation studies have been a powerful tool in evaluating and understanding decision-making and drug policy [30, 31]. We have included intercountry variation as a measure of the interplay between evidence based medicine and 'real life' practice. All else equal, one would expect the intercountry variation to be minimal for all drug classes if each country practiced perfect evidenced based medicine; this is obviously not the case. Even after attempting to minimize possible biases in the calculations of intercountry variation by selecting those therapeutic areas where the disease epidemiology should be similar across the four countries and by limiting the analysis only to reimbursed drugs, we have found substantial variation in drug utilization among these four countries. What have we learned from this? Scientific evidence is not by itself predictive of the use of drugs across countries, in fact, tradition, cultural beliefs, drug promotion, and pharmaceutical reimbursement structures play a substantial role in determining the utilization of drugs [2, 30, 32, 33]. Although the Treaty of Rome (EU harmonization agreement) [2] has focused mainly on the supply side, it may be worth addressing the issue of pharmaceutical demand variation across the European Union in the future.

Inter-country variation in reimbursement decisions for various products can be improved with increased transparency in the health policy decisions that are made on a country by country level. Building a better long-term partnership between health authorities, prescribing physicians, and pharmaceutical companies based on transparency and respect of indications would be beneficial from the patient point of view as well as from an economic point of view.

Several limitations of this analysis should be acknowledged. First, in our assessment of level of therapeutic evidence we focus on 'efficacy' rather than 'effectiveness' of each of the selected classes of drugs due to using the Cochrane Library as a main point of reference. Second, the social aspects as they pertain to patients (compliance and patient acceptance of new medical technologies) are not included in the analysis, but are recognized as major drivers for drug utilization. Third, the inclusion of only reimbursed drugs may have different meanings in different countries because of varying levels of reimbursement. Also, the classes of drugs included in our analysis represent only 21–36% of the total expenditure for reimbursed medicines in these countries, precluding generalizations of our interpretations to the entire drug budget. However, this analysis was conducted only to illustrate the perspective of the third party payer in charge of the drug budget, and it was believed that only drugs eligible for reimbursement would be of interest. Fourth, for simplicity, we have decided to dichotomize the level of efficacy and susceptibility of inappropriate prescribing knowing that these variables may vary over a wide range. This

classification may not actually capture the different levels of variability in those attributes. Fifth, a certain level of subjectiveness in the analysis of specific drug classes could not be avoided due to a lack of sufficient objective information. In the absence of established guidelines or well defined characteristics of drugs associated with a high level of inappropriate use, judgement on appropriateness of prescription is also subjective to some degree. However, we consistently classified only those drug classes as 'highly susceptible' for which there is convincing, published evidence of inappropriate use as defined above. Sixth, there is a certain level of dependence between the two axes of Figure 1. There is no doubt that the susceptibility of inappropriate prescribing will depend somewhat on the level of therapeutic evidence, however, for the purpose of this policy paper, we feel that it is appropriate to consider the two characteristics independently. Lastly, our analysis was conducted on a sample of outpatient prescription data, which might not be the best source for comparing drug utilizations across countries. However, the proposed approach could be expanded in those cases when more appropriate drug utilization data are present.

There is too much money tied up in the use of inefficient medicines requiring a need for reallocation of resources within the EU. Although the drug approval process has been harmonized almost completely with the EU, the differences in drug prescribing between individual countries remain striking [1, 31]. Strategies for controlling drug costs and maintaining adequate access to available drug products with proven patient benefit, have not shown satisfactorily results so far [3]. There is a clear need for visionary thinking in bridging the gap between the different interests of the various payers in the market place without losing the patient as our primary focus [33].

We presented a methodology in this paper that may be useful in helping policy-makers in building rationale for the confidence in new innovative strategies for appropriate resource allocation in pharmacotherapy. The level of therapeutic evidence should be the primary factor determining medication use, but that alone will not guarantee efficient allocation of resources, the susceptibility of inappropriate prescribing must be considered. Inter-country variation can be used as a prompt to monitor and re-evaluate the allocation of resources for pharmacotherapy. Inefficiencies in the spending of limited health care resources can be identified, and resources can be reallocated to products that have been shown to improve patient care through evidence based medicine.

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