Original Article

Matrix models as an instrument to support generic medicine prescribing

Received (in revised form): 8th July 2010

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ABSTRACT European countries have introduced various incentives to encourage physicians to prescribe generic medicines. This article aims to discuss matrix models, that is, decision tools to inform medicine prescribing in a transparent and reproducible way, and assess their implications for generic medicine use. To date, two types of matrix models, the System of Objectified Judgement Analysis and InforMatrix, have been introduced in the Netherlands; and the Safe Therapeutic Economic Pharmaceutical Selection (STEPSelect) method has been implemented in Northern Ireland. These matrix models in essence identify the most

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appropriate medicine to prescribe, taking into account clinically relevant and evidence-based selection criteria such as safety, efficacy, ease of use, tolerability, applicability and costs. As a result, matrix models are generally well accepted by both physicians and pharmacists. Generic medicines tend to receive favourable scores in matrix models because they have the same quality, safety and efficacy as originator medicines, but have a lower cost. In addition, the application of matrix models is estimated to generate substantial savings through, among other things, the increased prescribing of generic medicines. Future studies need to quantify the impact of matrix models on generic medicine prescribing rates.

Journal of Generic Medicines (2010) **7**, 334–341. doi:10.1057/jgm.2010.25; published online 31 August 2010

Keywords: generic medicines; prescribing; evidence-based medicine; matrix models

INTRODUCTION

The increased use of generic medicines plays a crucial role in creating sustainable health-care systems in Europe. However, Europe is not maximising the full potential of generic medicines.¹ By virtue of their prescribing, physicians play a key role in the development of a generic medicines market and consequently countries have introduced a variety of financial and non-financial incentives to encourage generic medicine prescribing.²

Some countries have experimented with budgets at regional level (for example Germany) or budgets at the level of an individual physician (for example the United Kingdom). Countries such as Denmark, the United Kingdom, the Netherlands and Portugal have attempted to stimulate generic medicines uptake through medicine prescribing using the international non-proprietary name. In addition, generic medicine prescribing by physicians has been supported in European countries by a variety of initiatives, including electronic prescribing systems, medicine databases, audit of and feedback on prescribing data, prescribing guidelines and formularies, and local pharmaco-therapeutic discussions between physicians and pharmacists.

Medicine prescribing is a complex process and should ideally be a rational process, based on evidence-based criteria such as clinical efficacy, safety, tolerability, medicine

interactions, dosage frequency and cost.

However, in practice, numerous other factors can play a role in medicine prescribing including practitioner experience, influence of pharmaceutical companies, financial interests, the scientific literature, guidelines, government/health insurance companies, the opinion of colleagues and patients.³ As a result, the medicine prescribing process is not always evidence-based, transparent or reproducible.

In the last 20 years, matrix models have been developed.⁴ Matrix models are decision tools to inform medicine prescribing in a transparent and reproducible way. A matrix model is in essence an interactive programme that identifies the most appropriate medicine to prescribe, taking into account clinically relevant and evidence-based selection criteria. Such matrix models have been implemented in the Netherlands⁴ and in Northern Ireland.⁵

As the introduction of matrix models is likely to have an impact on the prescribing of originator and generic medicines, the aim of this article is to describe the design of available matrix models and to assess the experience with these models to date. This will aid physicians, health insurance companies and policymakers in gaining a better understanding of how matrix models can support generic medicine prescribing and how matrix models can be used as a tool to support further population health improvements while optimising pharmaceutical expenditure.

MATRIX MODELS IN THE NETHERLANDS

Two different types of matrix models have been developed in the Netherlands: the System of Objectified Judgement Analysis (SOJA)⁴ and InforMatrix.⁶ These matrix models are used for assessing medicines within a certain pharmaceutical class.

The SOJA matrix model

The SOJA matrix model defines a number of selection criteria for a given group of medicines and scores the extent to which each individual medicine fulfils the requirements for each criterion. The selection criteria are: clinical efficacy, documented effects on clinically relevant endpoints, incidence and severity of side effects, dosage frequency, medicine interactions, costs, documentation and strength of evidence, pharmacokinetic and pharmaceutical aspects, and group-specific criteria (for example, development of resistance is considered for antibiotics). Each criterion is given a relative weight, that is, more important selection criteria are assigned a higher relative weight.

The scores of a medicine on each selection criterion are determined by a panel of experts in the field. The expert panel is as independent as possible and a standardised procedure is used in the assessment of the scientific correctness and completeness of the evidence. This procedure involves literature searches in relevant databases and publications; consultation of European Medicines Agency scientific reports and National Institute for Health and Clinical Excellence guidelines; and validation of the evidence by an editorial board, and all pharmaceutical companies active in the field 'for comments on scientific correctness and completeness'.

The scores of all medicines are compared to the hypothetical 'ideal' medicine from that group, which is assigned the full relative weight for each criterion. This medicine will be 100 per cent effective in

all patients, have optimal effects in terms of clinically relevant endpoints and quality of life, have no side effects, is given once daily, shows no medicine interactions, is well documented and has a low acquisition cost. The scores for the other medicines for each selection criterion are expressed as a percentage of the relative weight for that criterion. One medicine may therefore score 70 per cent on efficacy, 80 per cent for side effects, 100 per cent for dosage frequency, 30 per cent for medicine interactions and 20 per cent for cost, as compared with the 'ideal' medicine that is used as a reference.

In the published SOJA scores, 1000 points are divided over the criteria that are considered to be relevant for a particular group of medicines. In the interactive programme, the scores for each medicine have been determined by a panel of experts, but users of the programme (for example physicians, pharmacists) are free to assign their own relative weight to each criterion. The programme then computes the ranking scores for the medicines in the group.

The InforMatrix model

The InforMatrix model was developed in the early 1990s.⁷ The InforMatrix model is an instrument that enables the users of the programme to determine, on the basis of agreed criteria, an order of merit for the various medicines available in a specific category. The criteria used are effectiveness, safety, tolerability, ease of use, applicability and costs. Relative weights are applied to these six criteria by the users of the programme. Next, medicines are compared with each other per criterion. This evaluation of the medicines is informed by data from the literature and by clinical experience. The weighted score of a medicine per criterion is determined by multiplying the score of a medicine for the criterion by the relative weight of the criterion. To compute the final score of a medicine, the weighted scores are totalled across the six criteria.

Figure 1: Illustration of application of InforMatrix to antidepressants.

Figure 1 illustrates how InforMatrix was used by a panel of 104 physicians and pharmacists to score 14 antidepressants in terms of effectiveness, safety, tolerability, ease of use, applicability and costs. These data show that the overall assessment varied substantially between individual antidepressants, with citalopram receiving the highest total score and maprotiline receiving the lowest score. Furthermore, the highest scores were assigned to active substances for which generic medicines are available, such as citalopram, paroxetine, venlafaxine and mirtazapine. For instance, the total score of citalopram (for which generic medicines and an originator medicine exist) was higher than that of escitalopram (for which only an originator medicine exists). Please note that these sessions were done before the 2009 meta-analysis on antidepressant drugs was published in the *Lancet*.⁸

Comparison of SOJA and InforMatrix

A detailed discussion of the similarities and differences between the SOJA and InforMatrix models falls outside the scope of this manuscript,⁶ but some aspects relating to the choice of criteria and weighting are highlighted.

Both types of matrix models, in essence, calculate the score of a medicine for each criterion and then compute an overall score taking into account the relative weight of the criteria. Whereas the criteria of the InforMatrix model tend to be related to the disease process (for example applicability), the criteria used in the SOJA matrix model tend to be medicine related (for example pharmacokinetic aspects). In both types of matrix models, the users of the programme may assign their personal weight to each selection criterion. In SOJA, the score of a medicine for a selection criterion is judged by a panel of experts. InforMatrix is a blank matrix, in which the users of the programme have to judge both the weighting of the criteria as well as the score of a medicine for each criterion.

SOJA/InforMatrix and generic prescribing

The experience with the SOJA and InforMatrix models shows that users of the programme tend to assign high relative weights to criteria such as clinical efficacy, documented effects on clinical endpoints, safety and dosage frequency. Medicines that perform well on these criteria therefore show a high score for almost all users. In general,

Table 1: Highest-ranking generic medicines according to SOJA/InforMatrix

Pharmaceutical class	Medicines with highest ranking
ACE inhibitors in hypertension	Ramipril, enalapril, perindopril
Acute exacerbations of chronic bronchitis	Amoxicillin, doxycycline
Antidepressants	Paroxetine, mirtazapine, sertraline
Antiemetics in oncology	Ondansetron, granisetron
Antiemetics in surgery	Ondansetron, granisetron
Antipsychotics	Risperidone, haloperidol
Anxiety	Paroxetine
Benign prostatic hyperplasia	Tamsulosin, alfuzosin
Bipolar disorder	Lithium, risperidone
Calcium antagonists in hypertension	Amlodipine
Antidiabetic medicines	Metformin
Long-acting opiates in cancer pain	Fentanyl matrix
Nasal corticosteroids	Budesonide, fluticasone
Non-steroidal anti-inflammatory medicines	Diclofenac, ibuprofen, naproxen
Onychomycosis	Terbinafine
Osteoporosis	Alendronate
Reflux oesophagitis	Omeprazole
Statins	Simvastatin

generic medicines score very well in the SOJA and InforMatrix models. Their high scores do not so much originate from their low cost (as physicians and pharmacists do not consider cost to be an important criterion), but from their proven clinical efficacy, proven effects on clinically relevant endpoints (morbidity and mortality), extensive and long-term clinical experience with the medicine and documented long-term safety. Examples of pharmaceutical classes where generic medicines tend to perform well are presented in Table 1.

MATRIX MODELS IN NORTHERN IRELAND

The STEPSelect model

In Northern Ireland, the Safe Therapeutic Economic Pharmaceutical Selection method (STEPSelect) was developed.⁵ In this programme, matrix models (SOJA) were used in the first step to identify the most

efficacious medicines within a pharmaceutical class. In the second step of the STEPSelect process, the packaging of the selected medicines is judged using a standard regionally agreed template. This is followed by a budget impact analysis (third step) and a procurement selection (fourth step).

The key steps involved in the STEPS approach are summarised below:

- *STEP I – clinical evaluation:* Evaluation and updating of available evidence relating to efficacy, safety, tolerability, ease of use, medical interactions and experience is continuously carried out. Use of this information in matrix models to support the pre-selection of medicines within a pharmaceutical class is founded on clinical criteria only. The assessments are undertaken by an expert panel comprising consultants, general practitioners with special interests, clinical pharmacists, other health-care professionals as appropriate, and industry representatives as observers.
- *STEP II – risk assessment:* This step examines factors that could have an impact on the safety of medicines during routine use by patients. The risk assessment focuses on packaging and instructions with a view to minimising difficulties for patients and supporting the safe and optimal use of their medication.
- *STEP III – budget impact analysis:* This step explores the impact of the use of medicines in a pharmaceutical class on health expenditure. Reduced expenditure may arise from selecting the most cost-effective medicines to deliver the desired outcomes at minimised cost to the health-care system.
- *STEP IV – procurement selection:* Finally, only the top two or three medicines (usually) are chosen as the preferred medicines (and suppliers) in Northern Ireland taking into account the efficacy, safety, tolerability, ease of use, drug interactions, experience and budgetary impact of the medicines.

The STEPSelect model and generic prescribing

A pilot scheme was initiated in one Health Board (representing 25 per cent of the population) in Northern Ireland.⁵ The pilot scheme focused specifically on reaching agreement on product standardisation of generic medicines. Agreement was reached via the Northern Area Prescribing Forum, which represents all key stakeholders in the area (specialist physicians, general practitioners, hospital and community pharmacists and prescribing advisers) with regard to the use of seven branded generic medicines. These generic medicines were concluded to have equivalent clinical efficacy as the originator drugs on the basis of evidence. The medicines are listed in Table 2.

In primary care, prescribing advisers and prescribing support assistants actively promoted and implemented the change with general practitioners. Community pharmacists were also key players in this process with regard to availability and stock management. In secondary care, appropriate contractual arrangements were put in place by the Regional Pharmaceutical Procurement Unit, ensuring that the agreed products were utilised in hospital and detailed on discharge. This process proved to be very effective in achieving the objective of product standardisation, thereby eliminating the significant risk factor of presentation change and contributing to seamless care between the

secondary and primary sectors. In the pilot Health Board area, the current percentage of standardised medicines is in the range of 40–50 per cent as compared with 4–11 per cent in other Health Boards.

The STEPSelect approach is well accepted by both physicians and pharmacists because of the fact that product selection is based on clinically relevant criteria. In Northern Ireland, the application of matrix models to five major pharmaceutical classes has been estimated to generate annual savings through, among other things, the increased prescribing of generic medicines of £7.7 million for statins; £5.5 million for proton pump inhibitors; £2.0 million for selective serotonin re-uptake inhibitors; and £0.7 million for angiotensin-converting enzyme inhibitors. Based on a population of 1.7 million inhabitants, these savings would translate into an annual cost reduction of around £10 per capita.³

DISCUSSION

As physicians tend to have few incentives to prescribe generic medicines in most European countries,² this article has identified matrix models as an instrument to support generic medicine prescribing. Matrix models provide a tool to facilitate rational and evidence-based medicine prescribing. Such models can be applied by physicians, pharmacists, formulary committees in hospitals, health insurance companies and policymakers to inform medicine selection.

Matrix models ensure that medicine prescribing is founded on multiple rational and evidence-based criteria. Other non-rational selection criteria do not play a role in the decision-making process. As a result, medicine prescribing becomes transparent and reproducible as the criteria and weightings on which decisions are based are known. A matrix model also avoids the situation where a decision is taken solely on one criterion and, therefore, supports a comprehensive approach towards medicine prescribing. The use of matrix models in the Netherlands and

Table 2: Generic medicines used for product standardisation

<i>Current medicine</i>	<i>New medicine</i>
Calcichew, Shire	Adcal, ProStrakan
Imdur, Astra Zeneca; Elantan LA, Scharwz	Isotard XL, ProStrakan
Adalat LA, Bayer	Coracten XL, Celltech
Gaviscon, Reckitt-Benckiser	Peptac, Ivax
Nitrate patches, Deponit (Scharwz), Minitran (3M)	Nitrodur, Schering-Plough
Proctosedyl preparation, Aventis Pharma	Uniroid preparation, Chemidex
Diltiazem brands, various brands	Slozem, Merck

Northern Ireland has demonstrated that this method for medicine prescribing greatly aids the discussion in, for example, pharmacotherapy audit meetings between general practitioners and/or pharmacists, local or regional formulary committees, pricing and reimbursement negotiations.

Matrix models rely on the active participation of physicians, pharmacists and other stakeholders in informing medicine prescribing. These models tend to integrate 'top-down' and 'bottom-up' methods of decision making. The 'top-down' contents of matrix models (that is assessment of medicines based on a thorough evaluation of the evidence) are combined with the high compliance of the 'bottom-up' decision-making process as the final decision is made by, for example, the formulary committee in a hospital. This is likely to increase the acceptability of the outcome of a matrix model, namely the identification of the most appropriate medicine to prescribe.

Matrix models suffer from a number of limitations. Matrix models are time dependent in that the evidence on the efficacy, safety, costs, pharmacokinetic and pharmaceutical aspects and so on of medicines changes continuously. In addition, new products are introduced over time or are withdrawn from the market. Regular updates of the information needed by matrix models are therefore necessary. For instance, the Dutch SOJA matrix model is updated with new literature every 3 months and prices are updated every month.

Even though matrix models are a step towards objective medicine prescribing, it should be noted that there is some subjectivity involved in such models. For example, although there is usually agreement on the fact that medicine A has a lower incidence of side effects than medicine B as proven in clinical trials, any assessment of the importance of the observed difference is subjective. Therefore, a number of peer reviewers critically assess the evidence that is integrated in the SOJA matrix model. In

addition, matrix models present an order of merit for the various medicines available in a specific category based on an aggregate assessment of criteria such as effectiveness, safety, tolerability, ease of use, applicability and costs. There may be cases where a physician decides not to prescribe a high-ranking medicine for a specific patient due to expected side effects, even though the aggregate assessment of the safety profile is favourable. Matrix models are general decision tools to inform medicine prescribing, but the physician remains responsible for prescribing medicines to individual patients.

It could be argued that matrix models may inhibit the introduction of innovative medicines owing to the limited documentation of evidence on such medicines. If a new medicine has no added benefit as compared to existing medicines in terms of the selection criteria used in matrix models, it will almost certainly show a low score because of its poorer documentation and usually higher acquisition cost. However, such medicines are not innovative, but are in essence 'me too' medicines. A truly innovative medicine would exhibit an added benefit as compared to existing medicines, thus generating a high score in a matrix model.

The operation of matrix models in practice shows that users of the programme tend to assign high relative weights to the clinical efficacy, documented effects on clinical endpoints, safety and dosage frequency of medicines. Pharmaceutical factors, pharmacokinetics and acquisition cost are usually given a low relative weight. Generic medicines tend to receive favourable overall scores because they have the same quality, safety and efficacy as originator medicines, but have a lower cost.

Future research is needed to examine the impact of matrix models on generic medicine prescribing rates. In addition, studies are necessary to quantify the savings in pharmaceutical expenditure generated by matrix models. Such savings need to be

compared with the costs of implementing, operating and updating matrix models. Furthermore, the potential health impact of introducing matrix models needs to be considered. Therefore, an economic evaluation assessing the cost-effectiveness of matrix models is called for.

CONCLUSIONS

Matrix models may serve as an instrument to support generic medicine prescribing. The experience of the Netherlands and Northern Ireland indicates that generic medicines tend to perform well in matrix models. This is because generic medicines have the same quality, safety and efficacy as originator medicines, but are less expensive, thereby assisting in maximising patient benefit relative to health-care expenditure. Future studies need to quantify the impact of matrix models on generic medicine prescribing rates.

ACKNOWLEDGEMENTS

No sources of funding were used to assist in the preparation of this article. The authors have no conflicts of interest that are directly relevant to the content of this article.

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