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How matrix models can support generic medicine prescribing

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This paper describes the design of currently available matrix models and assesses the experience with these models to date. Matrix models provide a valuable tool to facilitate transparent and interactive evidence-based medicine prescribing. In many cases, generically available drugs perform well because of the documented effects on clinically relevant endpoints, good clinical efficacy, extensive experience, and documented long-term safety. Taking the lower acquisition cost of generic drugs into account as well, matrix models can be used effectively to promote the use of generic drugs.

Keywords: InforMatrix, matrix models, System of Objectified Judgement Analysis (SOJA)

Introduction

The increased use of generic medicines is one of the most important elements in terms of the creation and maintenance of sustainable healthcare systems in Europe. Generic medicine prescribing by physicians in European countries has been supported by a variety of initiatives. However, despite these efforts, the use of generic drugs is still limited in many countries. Policymakers, insurers, and governments have focused on the low cost of generic drugs, but most physicians do not consider cost to be an important criterion; they want to prescribe a drug which is primarily effective and safe.

Prescribing is a complex process and, ideally, should be a rational process based on evidence-based criteria such as clinical efficacy, safety, tolerability, drug interactions, dosage frequency and ultimately cost. However, in practice, numerous other factors can play a role in medicine prescribing including emotional factors, the influence of pharmaceutical companies, personal financial interests, and unconscious criteria [1]. 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 to inform decisions in medicine prescribing in a transparent and reproducible way [2]. A matrix model, in essence, is an interactive computer program 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 Netherlands [2] and in Northern Ireland, UK [3].

As the introduction of matrix models is likely to have an impact on the prescribing of originator and generic medicines, the aim of this paper 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 policy makers to gain a better understanding of both how matrix models can support generic medicine prescribing and how they can be used as a tool to support further population health improvements whilst optimising pharmaceutical expenditure.

Matrix models in The Netherlands

Two matrix models have been developed in The Netherlands: the System of Objectified Judgement Analysis (SOJA) [2] and InforMatrix [4]. 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 most important selection criteria are: clinical efficacy, documented effects on clinically relevant endpoints, incidence and severity of side effects, tolerability, dosage frequency, drug interactions, costs, and documentation. Each criterion is given a relative weight, i.e. 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 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 ideal medicine will be 100% 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 drug interactions, is well documented concerning randomised double-blind comparative clinical studies, has a very low acquisition cost, and there must be extensive clinical experience with the drug. 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% on efficacy, 80% for side effects, 100% for dosage frequency, 30% for medicine interactions, and 20% for cost, as compared with the 'ideal' medicine that is used as a reference.

In the published SOJA scores, 1,000 points are divided over the criteria that are considered to be relevant for a particular group of medicines. An example of a SOJA score for antipsychotics in the treatment of schizophrenia is presented in Table 1. Once generic olanzapine becomes available, this drug will also perform well in a future SOJA update.

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Table 1: SOJA score for antipsychotics based on the program authors' weightings

	Indications	Formulations	Bioavailability	Interactions	Frequency	Efficacy	Tolerability	Safety	Cost	Documentation	Total
Weight factor	15	30	25	85	90	310	110	145	95	95	1,000
Aripiprazole	11	18	20	51	90	149	94	123	10	79	645
Clozapine*	5	18	9	51	81	171	72	58	69	64	597
Haloperidol*	14	30	14	68	90	149	72	73	95	95	700
Olanzapine*	12	24	16	68	90	174	88	109	95	95	771
Paliperidone	11	18	14	51	90	149	88	109	10	40	579
Pimozide	11	18	0	26	90	146	72	58	92	48	559
Quetiapine	12	18	15	59	90	158	88	123	0	81	645
Risperidone*	13	27	17	59	81	171	88	116	95	95	762
Zuclopentixol	14	27	16	68	90	146	72	73	93	50	647

SOJA: System of Objectified Judgement Analysis; *generics.

Interactive program

In the interactive program, the percentages scores for each medicine per criterion have been determined by a panel of experts, but users of the program, e.g. physicians, pharmacists, are free to assign their own relative weight to each criterion. The program then computes the ranking scores for the medicines in the group.

The InforMatrix model

The InforMatrix model was developed in the early 1990s [5]. The InforMatrix model is an instrument that enables the users of the program 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. Safety refers to the incidence of severe to life-threatening side effects and tolerability the incidence of mild to moderate side effects, such as nausea, headache or skin reactions. Relative weights are applied to these six criteria by the users of the program. Next, the medicines are compared to 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 cri-

terion 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. The most important differences and similarities of both methods are summarised in Table 2.

Validation

Various validation steps are used for matrix productions. For InforMatrix, a standard set of criteria is used in all productions. The same is true for SOJA, although extra criteria may be added when this is considered relevant, such as risk of development of resistance to antibiotics.

All matrix authors are asked to provide information on links with pharmaceutical companies or other conflicts of interest, which may affect their judgement. All discussions with individual authors are visible to all other authors in order to improve a transparent decision-making process.

Matrix models are a step towards objective medicine prescribing, but it should be noted that there is still some subjectivity involved in these models. For example, although there is usu-

Table 2: Differences and similarities between the SOJA and the InforMatrix models

	SOJA	InforMatrix
Weighting	During a session the weighting for each criterion is assigned by the participants. The properties of each drug have been judged by a panel of experts.	During sessions the weighting for each criterion and the judgement of the properties of each drug are assigned by the participants.
Description of criteria	Drug-related, e.g. pharmacokinetics	Disease process-related, e.g. applicability
Target group	Formulary committees in hospitals, general practitioners, community pharmacists	Expert groups, and formulary committees in hospitals
Complexity	Very easy to perform. Once the members are familiar with the program, decisions can be made within ten minutes in an interactive session. No special knowledge required of the participants.	More time-consuming, because the participants have to judge both the criteria and the judgement of each individual drug on each criterion. Specific knowledge of the pharmaceutical group in question is necessary, otherwise 'garbage in, garbage out'. Important advantage: local acquisition cost in each hospital can be used instead of official acquisition cost.

SOJA: System of Objectified Judgement Analysis.

Table 3: Highest-ranking generic medicines according to SOJA/InforMatrix

Pharmaceutical class	Medicines with highest ranking
ACE inhibitors in hypertension	Ramipril, enalapril, perindopril
Attention deficit hyperactivity disorder	Methylphenidate immediate release
Acute exacerbations of chronic bronchitis	Amoxicillin, doxycycline
ADP antagonists	Clopidogrel
Angiotensin II antagonists	Losartan
Antidepressants	Paroxetine, mirtazapine, sertraline
Antidiabetic medicines	Metformin
Antiemetics in oncology	Ondansetron, granisetron
Antiemetics in surgery	Ondansetron, granisetron
Antiherpes drugs	Valaciclovir
Antipsychotics	Risperidone, haloperidol
Anxiety	Paroxetine
Benign prostatic hyperplasia	Tamsulosin, alfuzosin
Bipolar disorder	Lithium, risperidone
Calcium antagonists in hypertension	Amlodipine
Diabetic foot infections	Amoxicillin-clavulanic acid
Hypertension	Various generics
Long acting opiates in cancer pain	Fentanyl matrix
Nasal corticosteroids	Budesonide, fluticasone
Non-steroidal anti-inflammatory medicines	Diclofenac, meloxicam, naproxen
Onychomycosis	Terbinafine
Osteoporosis	Alendronate
Reflux oesophagitis	Omeprazole, pantoprazole
Restless legs syndrome	Ropirinol
Statins	Simvastatin

SOJA: System of Objectified Judgement Analysis.

ally 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, as is done in SOJA, is subjective. Therefore, a number of peer reviewers critically assess the evidence integrated in the matrix model. The matrix productions are sent to all pharmaceutical companies that are marketing drugs in that specific drug class (including generics) for their comments on the scientific correctness and completeness. All articles are then published in peer reviewed journals, necessitating comments by independent reviewers.

How SOJA and InforMatrix can influence generics prescribing

SOJA is designed for use in primary care and for drug classes with large numbers of randomised clinical trials, allowing judgement of the relative efficacy and safety. InforMatrix is used primarily in

hospital care and for drug classes for which few or no direct double-blind comparative studies have been performed, such as for the tumour necrosis factor-alpha blockers, which have only been compared to placebo, but not between the drugs.

The experience with the SOJA and InforMatrix models suggests that users of the program usually 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, generic medicines score very well in the SOJA and InforMatrix models. Their high scores do not originate from their low cost—as physicians and pharmacists do not consider cost to be an important criterion, but instead 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 perform well in the most recent updates of published SOJA scores are presented in Table 3. These scores are based on the weightings assigned by the authors of the original publications.

Discussion

As physicians tend to have few incentives to prescribe generic medicines in most European countries, this paper has identified matrix models to be 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 medicinal selection.

Matrix models ensure that medicine prescribing is founded upon 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 Northern Ireland suggests that this method for medicine prescribing greatly aids discussion in pharmacotherapy audit meetings between general practitioners and/or pharmacists, local or regional formulary committees, pricing, and reimbursement negotiations.

Matrix models allow 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, i.e. 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 matrix model's outcome—namely the identification of the most appropriate medicine to prescribe.

Matrix models suffer from a number of limitations; they are time-dependent in that the evidence on the efficacy, safety,

costs, pharmacokinetic and pharmaceutical aspects of medicines change continuously. Also, new products are introduced over time and older products 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 every six months.

It could be argued that matrix models may inhibit the introduction of innovative medicines due 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. Generically available drugs will show higher scores compared to the 'me too' drugs. A truly innovative medicine would exhibit an added benefit compared to existing medicines, thus generating a high score in a matrix model, especially when effects on clinically relevant endpoints have been documented.

The operation of matrix models in practice—based on unpublished results from hundreds of interactive sessions in The Netherlands and Northern Ireland—shows that users of the program 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. During these sessions, generic medicines showed favourable overall scores because they have the same quality, safety, and efficacy as originator medicines, but have a lower cost. Compared to newer drugs from the same class, they have the advantage of wider clinical experience, documented effects on clinical endpoints and better documentation concerning randomised controlled clinical trials.

Other scores such as for erythropoiesis-stimulating factors and granulocyte colony-stimulating factor showed favourable results for drugs, which are also available as biosimilars. Again, the preference for these drugs is based on quality aspects instead of cost. Therefore, matrix models may also be useful to promote the use of (good quality) biosimilars.

How to implement matrix models in other countries

A variety of interactive tools are available on the Internet [6], which allow active participation of physicians and pharmacists in the preparation of the score. The existing programs are specific for the Dutch and UK situation. Several adjustments to criteria need to be made to make these programs suitable for use in other countries such as available formulations, trade names, approved indications, dosage frequency, and acquisition cost. These adjustments can be made in a couple of hours per program, so country-specific matrices can be made at very short notice. Besides this, it is highly recommended to use a local expert group in each country to increase 'ownership'; transla-

tion into the local language is also recommended for most countries.

Conclusion

Matrix models may serve as an instrument to support generic medicine prescribing. The experience of The Netherlands and Northern Ireland indicates that generic medicines perform well in matrix models. In Northern Ireland, generic drugs showed the highest scores for the first five drug classes—statins, proton pump inhibitors, ACE inhibitors, angiotensin II antagonists, and selective serotonin reuptake inhibitors—investigated by the matrix methodology [7]. In the Dutch situation, generics showed the highest scores for many pharmaceutical classes. The main advantage of matrix models is that the high scores for drugs available as generics are based on clinically relevant criteria, such as efficacy, documented effects on clinical endpoints, safety and dosage frequency of medicines and not solely on acquisition cost. Therefore the outcomes of matrix models are accepted much better by physicians, rather than choosing generic drugs on the basis of cost. All matrices are available in an interactive format, thereby allowing active participation of physicians and pharmacists.

For patients

Use of generic drugs instead of patented drugs can save major amounts of money. However, many physicians do not consider cost an important selection criterion. This paper describes interactive matrix models to promote rational drug selection within a drug class, based on criteria such as efficacy, safety, tolerability, dosage frequency, drug interactions, documentation and cost. When all these criteria are taken into consideration and weighted, generic drugs are very interesting alternatives to much more expensive patented drugs.

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